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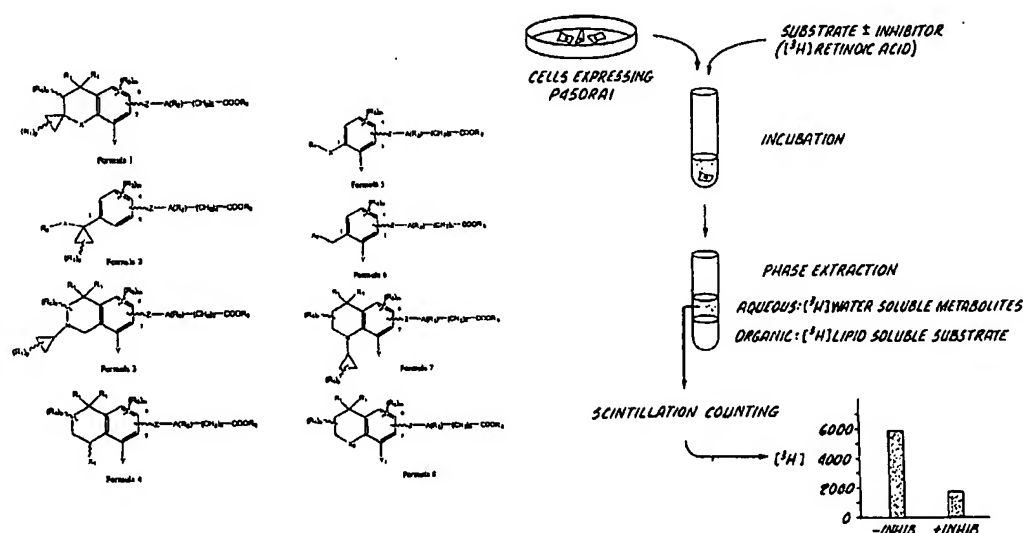
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(54) Title: **METHODS OF PROVIDING AND USING COMPOUNDS HAVING ACTIVITY AS INHIBITORS OF CYTOCHROME P450RA1**



1 METHODS OF PROVIDING AND USING COMPOUNDS HAVING
2 ACTIVITY AS INHIBITORS OF CYTOCHROME P450RAI

3 BACKGROUND OF THE INVENTION

4 1. Cross-Reference to Related Application

5 This application is a continuation-in-part of application serial number
6 09/651,235, filed August 29, 2000.

7 2. Field of the Invention

8 The present invention is directed to providing, preparing and using
9 compounds which inhibit the enzyme cytochrome P450RAI. More
10 particularly, the present invention is directed to selecting and preparing
11 compounds which inhibit the enzyme cytochrome P450RAI, many of which
12 are derivatives of phenylacetic or heteroarylacetic acid, and using said
13 compounds for treatment of diseases and conditions which are normally
14 treated by retinoids.

15 BACKGROUND ART

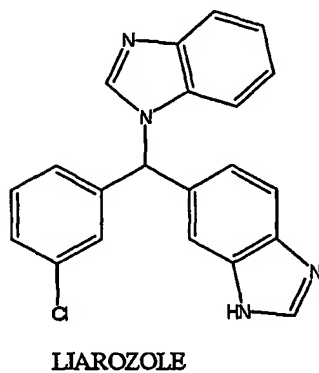
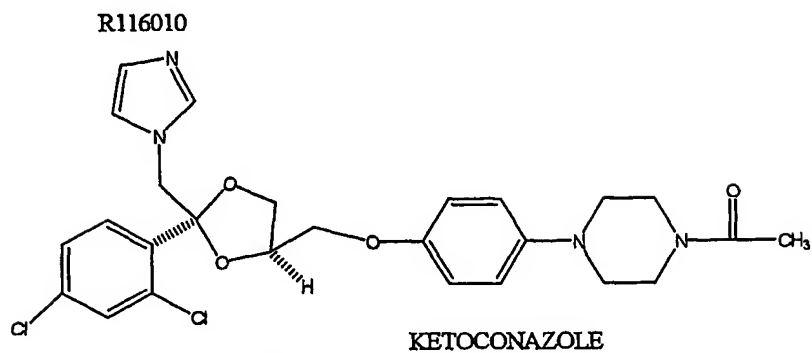
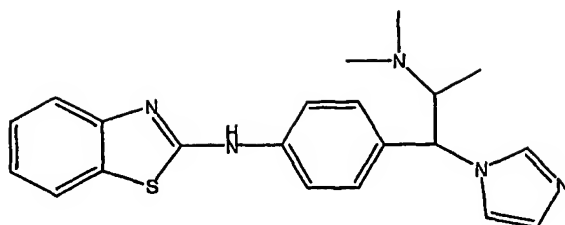
16 Compounds which have retinoid-like activity are well known in the art,
17 and are described in numerous United States and other patents and in scientific
18 publications. It is generally known and accepted in the art that retinoid-like
19 activity is useful for treating animals of the mammalian species, including
20 humans, for curing or alleviating the symptoms and conditions of numerous
21 diseases and conditions. In other words, it is generally accepted in the art that
22 pharmaceutical compositions having a retinoid-like compound or compounds
23 as the active ingredient are useful as regulators of cell proliferation and
24 differentiation, and particularly as agents for treating skin-related diseases,
25 including, actinic keratoses, arsenic keratoses, inflammatory and
26 non-inflammatory acne, psoriasis, ichthyoses and other keratinization and
27 hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers
28 disease, lichen planus, prevention and reversal of glucocorticoid damage
29 (steroid atrophy), as a topical anti-microbial, as skin anti-pigmentation agents

1 and to treat and reverse the effects of age and photo damage to the skin.
2 Retinoid compounds are also useful for the prevention and treatment of
3 cancerous and precancerous conditions, including, premalignant and malignant
4 hyperproliferative diseases such as cancers of the breast, skin, prostate, cervix,
5 uterus, colon, bladder, esophagus, stomach, lung, larynx, oral cavity, blood
6 and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias and
7 papillomas of the mucous membranes and in the treatment of Kaposi's
8 sarcoma. In addition, retinoid compounds can be used as agents to treat
9 diseases of the eye, including, without limitation, proliferative
10 vitreoretinopathy (PVR), retinal detachment, dry eye and other corneopathies,
11 as well as in the treatment and prevention of various cardiovascular diseases,
12 including, without limitation, diseases associated with lipid metabolism such
13 as dyslipidemias, prevention of post-angioplasty restenosis and as an agent to
14 increase the level of circulating tissue plasminogen activator (TPA). Other
15 uses for retinoid compounds include the prevention and treatment of
16 conditions and diseases associated with human papilloma virus (HPV),
17 including warts and genital warts, various inflammatory diseases such as
18 pulmonary fibrosis, ileitis, colitis and Krohn's disease, neurodegenerative
19 diseases such as Alzheimer's disease, Parkinson's disease and stroke, improper
20 pituitary function, including insufficient production of growth hormone,
21 modulation of apoptosis, including both the induction of apoptosis and
22 inhibition of T-Cell activated apoptosis, restoration of hair growth, including
23 combination therapies with the present compounds and other agents such as
24 Minoxidil^R, diseases associated with the immune system, including use of the
25 present compounds as immunosuppressants and immunostimulants,
26 modulation of organ transplant rejection and facilitation of wound healing,
27 including modulation of chelosis. Retinoid compounds have relatively
28 recently been also discovered to be useful for treating type II non-insulin

1 dependent diabetes mellitus (NIDDM).

2 Several compounds having retinoid-like activity are actually marketed
3 under appropriate regulatory approvals in the United States of America and
4 elsewhere as medicaments for the treatment of several diseases responsive to
5 treatment with retinoids. Retinoic acid (RA) itself is a natural product,
6 biosynthesized and present in a multitude of human and mammalian tissues
7 and is known to play an important rule in the regulation of gene expression,
8 tissue differentiation and other important biological processes in mammals
9 including humans. Relatively recently it has been discovered that a catabolic
10 pathway in mammals, including humans, of natural retinoic acid includes a
11 step of hydroxylation of RA catalyzed by the enzyme Cytochrome P450RAI
12 (retinoic acid inducible).

13 Several inhibitors of CP450RAI have been synthesized or discovered in
14 the prior art, among the most important ones ketoconazole, liarozole and
15 R116010 are mentioned. The chemical structures of these prior art compounds
16 are provided below. It has also been noted in the prior art, that administration
17 to mammals, including humans, of certain inhibitors of CP-450RAI results in
18 significant increase in endogeneous RA levels, and further that treatment with
19 CP450RAI inhibitors, for example with liarozole, gives rise to effects similar
20 to treatment by retinoids, for example amelioration of psoriasis.



1 The following publications describe or relate to the above-summarized
2 role of CP450RAI in the natural catabolism of RA, to inhibitors of CP-450RAI
3 and to *in vitro* and *in vivo* experiments which demonstrate that inhibition of
4 CP450RAI activity results in a increases endogeneous RA levels and potential
5 therapeutic benefits:

6 *Kuijpers, et al.*, "The effects of oral liarozole on epidermal proliferation and
7 differentiation in severe plaque psoriasis are comparable with those of
8 acitretin", British Journal of Dermatology, (1998) **139**: pp 380-389.

9 *Kang, et al.*, "Liarozole Inhibits Human Epidermal Retinoid Acid 4-
10 Hydroxylase Activity and Differentially Augments Human Skin Responses to
11 Retinoic Acid and Retinol *In Vivo*", The Journal of Investigative Dermatology,
12 (August 1996) **Vol. 107**, No. 2: pp 183-187.

13 *VanWauwe, et al.*, "Liarozole, an Inhibitor of Retinoic Acid Metabolism,
14 Exerts Retinoid-Mimetic Effects *in Vivo*", The Journal of Pharmacology and
15 Experimental Therapeutics, (1992) **Vol. 261**, No 2: pp 773-779.

16 *De Porre, et al.*, "Second Generation Retinoic Acid Metabolism Blocking
17 Agent (Ramba) R116010: Dose Finding in Healthy Male Volunteers",
18 University of Leuven, Belgium, pp 30.

19 *Wauwe, et al.*, "Ketoconazole Inhibits the *in Vitro* and *in Vivo* Metabolism of
20 All-*Trans*-Retinoic Acid", The Journal of Pharmacology and Experimental
21 Therapeutics, (1988) **Vol. 245**, No. 2: pp 718-722.

22 *White, et al.*, "cDNA Cloning of Human Retinoic Acid-metabolizing Enzyme
23 (hP450RAI) Identifies a Novel Family of Cytochromes P450 (CYP26)*", The
24 Journal of Biological Chemistry, (1997) **Vol. 272**, No. 30, Issue of July 25 pp
25 18538-18541.

26 *Hanzlik, et al.*, "Cyclopropylamines as Suicide Substrates for Cytochromes
27 P450RAI", Journal of Medicinal Chemistry (1979), **Vol. 22**, No. 7, pp 759-
28 761.

1 *Ortiz de Montellano*, "Topics in Biology - The Inactivation of Cytochrome
2 P450RAI", Annual Reports in Medicinal Chemistry, (1984), Chapter 20, pp
3 201-210.

4 *Hanzlik, et al.* "Suicidal Inactivation of Cytochrome P450RAI by
5 Cyclopropylamines> Evidence for Cation-Radical Intermediates", J. Am.
6 Chem. Soc., (1982), Vol. 104, No. 107, pp. 2048-2052.

7 In accordance with the present invention several previously known and
8 several new compounds are utilized as inhibitors of CP450RAI to provide
9 therapeutic benefit in the treatment or prevention of the diseases and
10 conditions which respond to treatment by retinoids and or which in healthy
11 mammals, including humans, are controlled by natural retinoic acid. The
12 perceived mode of action of these compounds is that by inhibiting the enzyme
13 CP450RAI that catabolyzes natural RA, endogenous RA level is elevated to a
14 level where desired therapeutic benefits are attained. The chemical structures
15 of certain previously known compounds which have been discovered to be
16 inhibitors of the enzyme CP450RAI are provided in the descriptive portion of
17 this application for patent. The chemical structures of the novel compounds
18 which are used in the methods of treatment in accordance with the invention
19 are summarized by **Formulas 1 through 8** in the Summary Section of this
20 application for patent. Based on these chemical structures the following art is
21 of interest as background to the novel structures.

22 U.S. Patent Nos. 5,965,606; 6,025,388; 5,773,594; 5,675,024;
23 5,663,347; 5,045,551; 5,023,341; 5,264,578; 5,089,509; 5,616,712; 5,134,159;
24 5,346,895; 5,346,915; 5,149,705; 5,399,561; 4,980,369; 5,015,658; 5,130,335;
25 4,740,519; 4,826,984; 5,037,825; 5,466,861; WO 85/00806; EP 0 130,795;
26 DE 3316932; DE 3708060; *Dawson, et al.* "Chemistry and Biology of
27 Synthetic Retinoids", published by CRC Press, Inc., (1990), pages 324-356;
28 are of interest to compounds of **Formula 1**.

1 U.S. Patent Nos. 5,965,606; 5,534,641; 5,663,357; 5,013,744;
2 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795; 4,992,468; 4,723,028;
3 4,855,320; 5,563,292; WO 85/04652; WO 91/16051; WO 92/06948; EP
4 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020; EP 0 619 116;
5 DE 3524199; Derwent JP6072866; *Dawson, et al.* "Chemistry and Biology of
6 Synthetic Retinoids", published by CRC Press, Inc., 1990, pages 324-356; are
7 of interest to compounds of **Formula 2**.

8 *Dawson, et al.* "Chemistry and Biology of Synthetic Retinoids",
9 published by CRC Press, Inc., (1990), pages 324-356; is of interest to
10 compounds of **Formula 3**.

11 U.S. Patent Nos. 5,965,606; 5,773,594; 5,675,024; 5,663,347;
12 5,023,341; 5,264,578; 5,089,509; 5,149,705; 5,130,335; 4,740,519; 4,826,969;
13 4,833,240; 5,037, 825; 5,466,861; 5,559,248; WO 85/00806; WO 92/06948;
14 WO 95/04036; WO 96/05165; EP 0 098 591; EP 0 170 105; EP 0 176 034;
15 EP 0 253,302; EP 0 303 915; EP 0 514 269; EP 0 617 020; EP 0 619 116;
16 EP 0 661 259; DE 3316932; DE 3602473; DE 3715955; UK application
17 GB 2190378; *Eyrolles et al.*, J. Med. Chem., (1994), **37**, 1508-1517; *Graupner*
18 *et al.* Biochem. and Biophysical Research Communications, (1991), 1554-
19 1561; *Kagechika, et al.*, J. Med. Chem., (1988), **31**, 2182-2192; *Dawson, et*
20 *al.* "Chemistry and Biology of Synthetic Retinoids", published by CRC Press,
21 Inc., (1990), pages 324-356; are of interest to compounds of **Formula 4**.

22 U.S. Patent Nos. 5,965,606; 6,025,388; 5,534,641; 5,663,357;
23 5,013,744; 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795; 4,992,468;
24 5,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;
25 WO 92/06948; EP 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;
26 EP 0 619 116; DE 3524199; Derwent JP6072866; *Dawson, et al.* "Chemistry
27 and Biology of Synthetic Retinoids", published by CRC Press, Inc., (1990),
28 pages 324-356; are of interest to compounds of **Formula 5**.

1 U.S. Patent Nos. 5,965,606; 6,025,388; 5,534,641; 5,663,357;
2 5,013,744; 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795; 4,992,468;
3 5,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;
4 WO 92/06948; EP 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;
5 EP 0 619 116; DE 3524199; Derwert JP6072866; *Dawson, et al.* "Chemistry
6 and Biology of Synthetic Retinoids", published by CRC Press, Inc., (1990),
7 pages 324-356; are of interest to compounds of **Formula 6**.

8 U.S. Patent Nos. 6,048,873; 5,663,347; 5,045,551; 5,023,341;
9 5,739,338; 5,264,578; 5,089,509; 5,616,712; 5,399,561; 4,826,984; 5,037,825;
10 EP 0 130 795; DE 3316932; *Dawson, et al.* "Chemistry and Biology of
11 Synthetic Retinoids", published by CRC Press, Inc., (1990), pages 324-356;
12 are of interest to compounds of **Formula 7**.

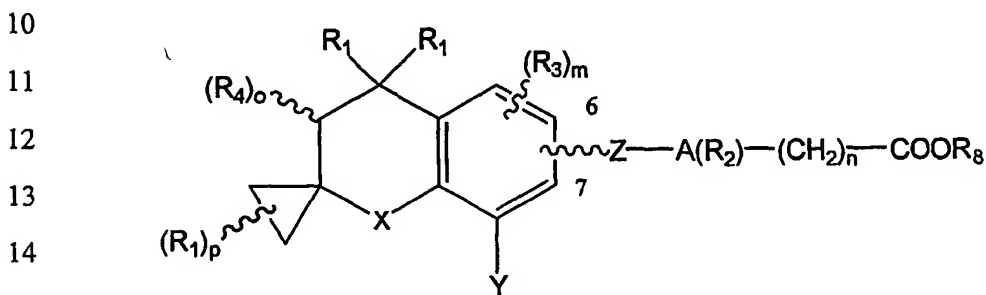
13 U.S. Patent Nos. 5,965,606; 5,998,471; 5,773,594; 5,675,024;
14 5,663,347; 5,045,551; 5,023,341; 5,264,578; 5,134,159; 5,346,895; 5,346,915;
15 5,149,705; 5,399,561; 4,980,369; 5,130,335; 4,326,055; 4,539,154; 4,740,519;
16 4,826,969; 4,826,984; 4,833,240; 5,037,825; 5,466,861; 5,559,248;
17 WO 85/00806; WO 92/06948; WO 95/04036; WO 96/05165; EP 0 098 591;
18 EP 0 130 795; EP 0 176 034; EP 0 253 302; EP 0 303 915; EP 0 514 269;
19 EP 0 617 020; EP 0 619 116; EP 0 661 259; DE 3316932; DE 3602473;
20 DE 3708060; DE 3715955; U.K. application GB 2190378; *Eyrolles et al.*, J.
21 Med. Chem., (1994), 37 1508, 1517; *Graupner et al.*, Biochem. and
22 Biophysical Research Communications, (1991) 1554-1561; *Kagechika, et al.*,
23 J. Med. Chem., (1988), 31, 2182-2192; *Dawson, et al.* "Chemistry and
24 Biology of Synthetic Retinoids", published by CRC Press, Inc., (1990), pages
25 324-356; are of interest to compounds of **Formula 8**.

26 Prior art which is of interest as background to the previously known
27 compounds that have been discovered in accordance with the present invention
28 to be inhibitors of cytochrome P450RAI, is identified together with the

1 identification of these known compounds.

2 SUMMARY OF THE INVENTION

3 In accordance with the present invention novel compounds of
 4 **Formulas 1** through **8** are used as inhibitors of the enzyme cytochrome
 5 P450RAI to treat diseases and conditions which are normally responsible to
 6 treatment by retinoids, or which are prevented, treated, ameliorated, or the
 7 onset of which is delayed by administration of retinoid compounds or by the
 8 mammalian organism's naturally occurring retinoic acid. These novel
 9 compounds are shown by **Formulas 1**



16 **Formula 1**

17
 18 wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from a group
 19 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
 20 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
 21 groups being optionally substituted with one or two **R₂** groups;

22 **X** is O, S or NR where **R** is H, alkyl of 1 to 6 carbons or benzyl;

23 **Y** is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
 24 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
 25 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

26 **Z** is $-C\equiv C-$,

27 $-(CR_1=CR_1)_{n'}$, where n' is an integer having the value 1 - 5,

28 $-CO-NR_1-$,

1 NR₁-CO-;

2 -CO-O-,

3 -O-CO-,

4 -CS-NR₁-,

5 NR₁-CS-,

6 -CO-S-,

7 -S-CO-,

8 -N=N-;

9 R₁ is independently H or alkyl of 1 to 6 carbons;

10 p is an integer having the values of 0 to 4;

11 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro
12 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
13 to 6 carbons;

14 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
15 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
16 of 1 to 6 carbons or benzyl;

17 m is an integer having the values 0 to 2;

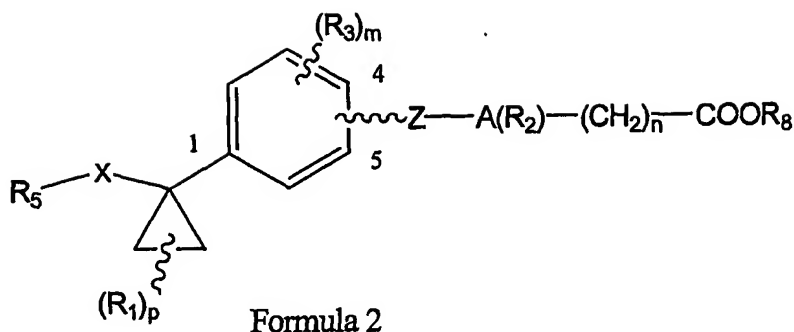
18 R₄ is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
19 alkyl of 1 to 6 carbons, or halogen;

20 o is an integer having the values of 0 to 2;

21 n is an integer having the values of 0 to 4, and

22 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
23 pharmaceutically acceptable base.

24 The novel compounds used in the method of treatment of the present
25 invention are also shown in **Formula 2**



wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;

Z is $-C\equiv C-$,

$-(CR_1=CR_1)_{n'}$, where n' is an integer having the value 1 - 5,

$-CO-NR_1-$,

NR_1-CO- ,

$-CO-O-$,

$-O-CO-$,

$-CS-NR_1-$,

NR_1-CS- ,

$-CO-S-$,

$-S-CO-$,

$-N=N-$;

R_1 is independently H or alkyl of 1 to 6 carbons;

p is an integer having the values of 0 to 4;

R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro

substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1

1 to 6 carbons;

2 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
3 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
4 of 1 to 6 carbons or benzyl;

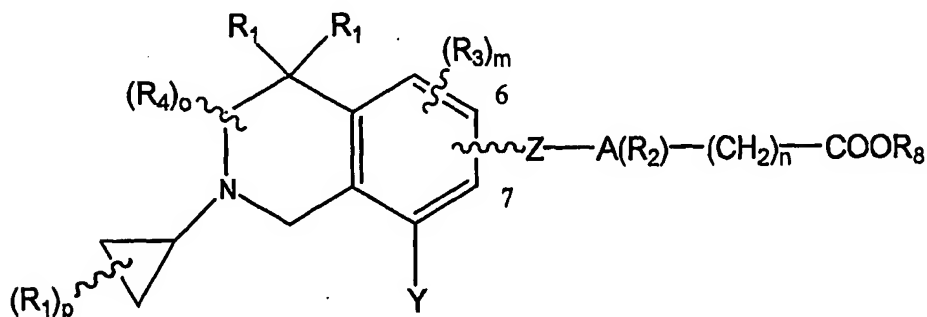
5 m is an integer having the values 0 to 4;

6 R_5 is H, alkyl of 1 to 6 carbons, fluorosubstituted alkyl of 1 to 6
7 carbons, benzyl, or lower alkyl or halogen substituted benzyl;

8 n is an integer having the values of 0 to 4, and

9 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
10 pharmaceutically acceptable base.

11 The novel compounds used in the method of treatment of the present
12 invention are also shown in **Formula 3**

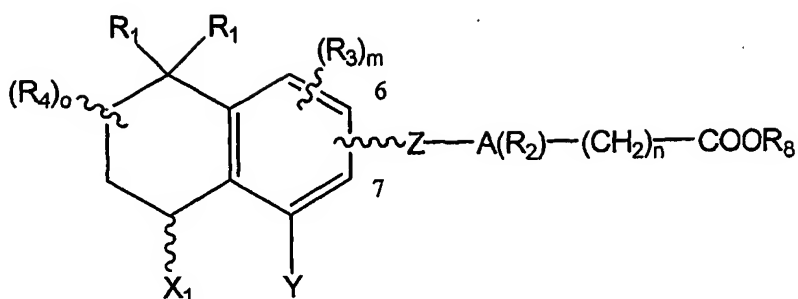


21 **Formula 3**

22 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
23 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
24 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl
25 groups being optionally substituted with one or two R_2 groups;

26 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
27 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
28 to 6 carbons, lower alkyl substituted cycloalkyl of 1 to 6 carbons, Cl, Br, or I;

- 1 **Z** is $-\text{C}\equiv\text{C}-$,
2 $-(\text{CR}_1=\text{CR}_1)_{n'}$, where n' is an integer having the value 1 - 5,
3 $-\text{CO}-\text{NR}_1-$,
4 $\text{NR}_1-\text{CO}-$,
5 $-\text{CO}-\text{O}-$,
6 $-\text{O}-\text{CO}-$,
7 $-\text{CS}-\text{NR}_1-$,
8 $\text{NR}_1-\text{CS}-$,
9 $-\text{CO}-\text{S}-$,
10 $-\text{S}-\text{CO}-$,
11 $-\text{N}=\text{N}-$;
12 **R**₁ is independently H or alkyl of 1 to 6 carbons;
13 **p** is an integer having the values of 0 to 5;
14 **R**₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
15 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
16 to 6 carbons;
17 **R**₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
18 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
19 of 1 to 6 carbons or benzyl;
20 **m** is an integer having the values 0 to 2;
21 **R**₄ is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
22 alkyl of 1 to 6 carbons, or halogen;
23 **o** is an integer having the values of 0 to 4;
24 **n** is an integer having the values of 0 to 4, and
25 **R**₈ is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
26 pharmaceutically acceptable base.
27 The novel compounds used in the method of treatment of the present
28 invention are also shown in **Formula 4**



Formula 4

wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

X_1 is 1-imidazolyl, or lower alkyl or halogen substituted 1-imidazolyl, OR, SR, NRR_6 where R is H, alkyl of 1 to 6 carbons or benzyl;

Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

Z is $-C\equiv C-$,

$-(CR_1=CR_1)_{n'}$, where n' is an integer having the value 1 - 5,

$-CO-NR_1-$,

NR_1-CO- ,

$-CO-O-$,

$-O-CO-$,

$-CS-NR_1-$,

NR_1-CS- ,

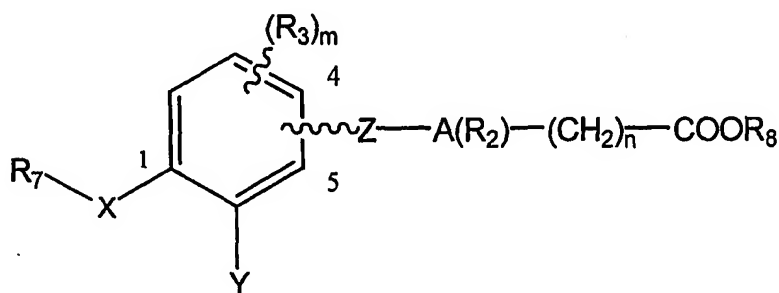
$-CO-S-$,

$-S-CO-$,

$-N=N-$;

R_1 is independently H or alkyl of 1 to 6 carbons;

- 1 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
 2 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
 3 to 6 carbons;
 4 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
 5 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
 6 of 1 to 6 carbons or benzyl;
 7 m is an integer having the values 0 to 2;
 8 R_4 is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
 9 alkyl of 1 to 6 carbons, or halogen;
 10 o is an integer having the values of 0 to 4;
 11 R_6 is H, lower alkyl, cycloalkyl of 3 to 6 carbons, lower alkyl
 12 substituted cycloalkyl of 3 to 6 carbons;
 13 n is an integer having the values of 0 to 4, and
 14 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
 15 pharmaceutically acceptable base, with the proviso that when Y is H, A is
 16 phenyl and X_1 is OH then n is 1 to 4.
 17 The novel compounds used in the method of treatment of the present
 18 invention are also shown in **Formula 5**



Formula 5

1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
2 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
3 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
4 groups being optionally substituted with one or two R_2 groups;

5 X is O, S or NR where R is H, alkyl of 1 to 6 carbons, C_{1-6} -trialkylsilyl
6 or benzyl;

7 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
8 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
9 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

10 Z is $-C\equiv C-$,

11 $-(CR_1=CR_1)_{n'}$, where n' is an integer having the value 1 - 5,

12 $-CO-NR_1-$,

13 NR_1-CO- ,

14 $-CO-O-$,

15 $-O-CO-$,

16 $-CS-NR_1-$,

17 NR_1-CS- ,

18 $-CO-S-$,

19 $-S-CO-$,

20 $-N=N-$;

21 R_1 is independently H or alkyl of 1 to 6 carbons;

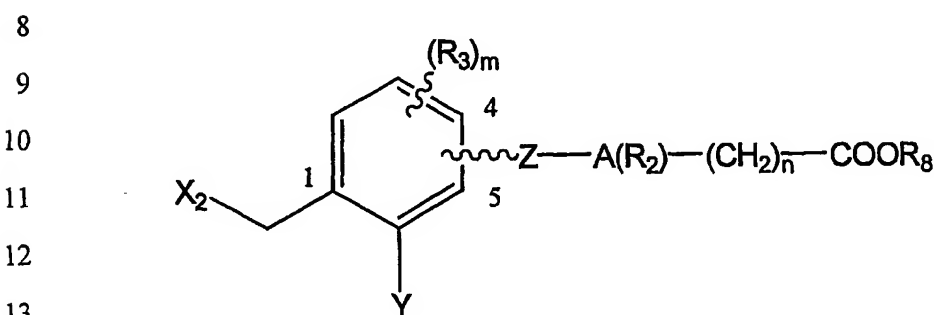
22 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
23 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
24 to 6 carbons;

25 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
26 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
27 of 1 to 6 carbons or benzyl;

28 m is an integer having the values 0 to 3;

1 R_7 is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or lower
 2 alkyl substituted cycloalkyl of 1 to 6 carbons;
 3 n is an integer having the values of 1 to 4, and
 4 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
 5 pharmaceutically acceptable base.

6 The novel compounds used in the method of treatment of the present
 7 invention are also shown in **Formula 6**



14 **Formula 6**

15 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
 16 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
 17 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl
 18 groups being optionally substituted with one or two R_2 groups;

19 X_2 is 1-imidazolyl, lower alkyl or halogen substituted 1-imidazolyl,
 20 OR_7 , SR_7 or NRR_7 where R is H, alkyl of 1 to 6 carbons or benzyl;

21 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
 22 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
 23 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

24 Z is $-\text{C}\equiv\text{C}-$,
 25 $-(\text{CR}_1=\text{CR}_1)_{n'}$, where n' is an integer having the value 1 - 5,
 26 $-\text{CO}-\text{NR}_1-$,
 27 $\text{NR}_1-\text{CO}-$,
 28 $-\text{CO}-\text{O}-$,

1 -O-CO-,

2 -CS-NR₁-,

3 NR₁-CS-,

4 -CO-S-,

5 -S-CO-,

6 -N=N-;

7 R₁ is independently H or alkyl of 1 to 6 carbons;

8 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
9 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
10 to 6 carbons;

11 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
12 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
13 of 1 to 6 carbons or benzyl;

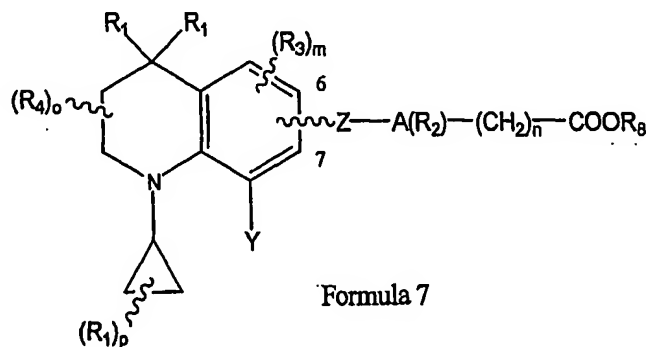
14 m is an integer having the values 0 to 3;

15 R₇ is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, lower
16 alkyl substituted cycloalkyl of 3 to 6 carbons or C₁₋₆-trialkylsilyl.

17 n is an integer having the values of 0 to 4, and

18 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
19 pharmaceutically acceptable base.

20 The novel compounds used in the method of treatment of the present
21 invention are also shown in Formula 7



1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
2 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
3 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
4 groups being optionally substituted with one or two R_2 groups;

5 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
6 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
7 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, F, Cl, Br, or
8 I;

9 Z is $-C\equiv C-$,
10 $-(CR_1=CR_1)_n$, where n' is an integer having the value 1 - 5,
11 $-CO-NR_1-$,
12 NR_1-CO- ,
13 $-CO-O-$,
14 $-O-CO-$,
15 $-CS-NR_1-$,
16 NR_1-CS- ,
17 $-CO-S-$,
18 $-S-CO-$,
19 $-N=N-$;

20 R_1 is independently H or alkyl of 1 to 6 carbons;

21 p is an integer having the values of 0 to 5;

22 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro
23 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
24 to 6 carbons;

25 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro
26 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
27 of 1 to 6 carbons or benzyl;

28 m is an integer having the values 0 to 2;

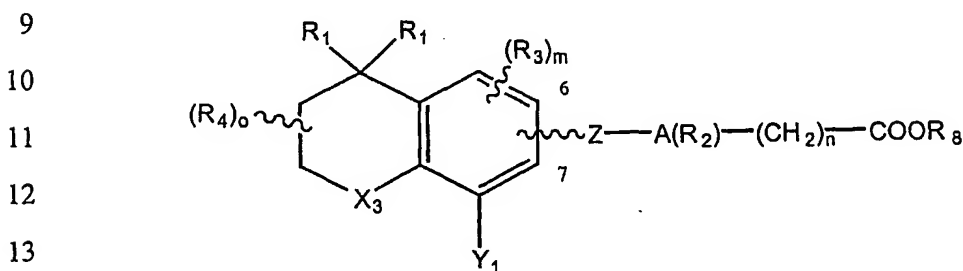
1 R_4 is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
2 alkyl of 1 to 6 carbons, or halogen;

3 o is an integer having the values of 0 to 4;

4 n is an integer having the values of 0 to 4, and

5 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
6 pharmaceutically acceptable base.

7 The novel compounds used in the method of treatment of the present
8 invention are also shown in Formula 8



Formula 8

15 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
16 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
17 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
18 groups being optionally substituted with one or two R_2 groups;

19 X_3 is S, or O, $\text{C}(\text{R}_1)_2$, or CO;

20 Y_1 is H, lower alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons,
21 benzyl, lower alkyl substituted cycloalkyl of 3 to 6 carbons;

22 Z is $-\text{C}\equiv\text{C}-$,

23 $-(\text{CR}_1=\text{CR}_1)_{n'}$, where n' is an integer having the value 1 - 5,

24 $-\text{CO}-\text{NR}_1-$,

25 $\text{NR}_1-\text{CO}-$,

26 $-\text{CO}-\text{O}-$,

27 $-\text{O}-\text{CO}-$,

28 $-\text{CS}-\text{NR}_1-$,

1 NR₁-CS-,

2 -CO-S-,

3 -S-CO-,

4 -N=N-;

5 R₁ is independently H or alkyl of 1 to 6 carbons;

6 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro
7 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
8 to 6 carbons;

9 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro
10 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
11 of 1 to 6 carbons or benzyl;

12 m is an integer having the values 0 to 2;

13 R₄ is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
14 alkyl of 1 to 6 carbons, or halogen;

15 o is an integer having the values of 0 to 4;

16 n is an integer having the values of 0 to 4, and

17 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
18 pharmaceutically acceptable base, the compound meeting at least one of the
19 provisos selected from the group consisting of:

20 Y₁ is cycloalkyl,

21 when Y₁ is not cycloalkyl then X₃ is O or S and n is 1,

22 when Y₁ is not cycloalkyl then X₃ is CO, and n is 1,

23 when Y₁ is not cycloalkyl then X₃ is CO and the moiety A is
24 substituted with at least one F group.

25 In accordance with the invention the novel compounds of **Formula 1**
26 through **Formula 8** as well as the previously known compounds disclosed
27 below in the specification are used for the prevention or treatment of diseases
28 and conditions in mammals, including humans, those diseases or conditions

1 that are prevented, treated, ameliorated, or the onset of which is delayed by
2 administration of retinoid compounds or by the mammalian organism's
3 naturally occurring retinoic acid. Because the compounds act as inhibitors of
4 the breakdown of retinoic acid, the invention also relates to the use of the
5 compounds of **Formula 1** through **Formula 8** in conjunction with retinoic
6 acid or other retinoids. In this regard it is noted that retinoids are useful for
7 the treatment of skin-related diseases, including, without limitation, actinic
8 keratoses, arsenic keratoses, inflammatory and non-inflammatory acne,
9 psoriasis, ichthyoses and other keratinization and hyperproliferative disorders
10 of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus,
11 prevention and reversal of glucocorticoid damage (steroid atrophy), as a
12 topical anti-microbial, as skin anti-pigmentation agents and to treat and reverse
13 the effects of age and photo damage to the skin. The retinoids are also useful
14 for the prevention and treatment of metabolic diseases such as type II non-
15 insulin dependent diabetes mellitus (NIDDM) and for prevention and
16 treatment of cancerous and precancerous conditions, including, premalignant
17 and malignant hyperproliferative diseases such as cancers of the breast, skin,
18 prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral
19 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,
20 leukoplakias and papillomas of the mucous membranes and in the treatment of
21 Kaposi's sarcoma. Retinoids can also be used as agents to treat diseases of the
22 eye, including, without limitation, proliferative vitreoretinopathy (PVR),
23 retinal detachment, dry eye and other corneopathies, as well as in the treatment
24 and prevention of various cardiovascular diseases, including, without
25 limitation, diseases associated with lipid metabolism such as dyslipidemias,
26 prevention of post-angioplasty restenosis and as an agent to increase the level
27 of circulating tissue plasminogen activator (TPA). Other uses for retinoids
28 include the prevention and treatment of conditions and diseases associated

1 with human papilloma virus (HPV), including warts and genital warts, various
2 inflammatory diseases such as pulmonary fibrosis, ileitis, colitis and Krohn's
3 disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's
4 disease and stroke, improper pituitary function, including insufficient
5 production of growth hormone, modulation of apoptosis, including both the
6 induction of apoptosis and inhibition of T-Cell activated apoptosis, restoration
7 of hair growth, including combination therapies with the present compounds
8 and other agents such as Minoxidil^R, diseases associated with the immune
9 system, including use of the present compounds as immunosuppressants and
10 immunostimulants, modulation of organ transplant rejection and facilitation of
11 wound healing, including modulation of chelosis.

12 This invention also relates to a pharmaceutical formulation comprising
13 one or more compounds of **Formula 1** through **Formula 8** or one or more of
14 the previously known compounds disclosed below in the specification, in
15 admixture with a pharmaceutically acceptable excipient, said formulation
16 being adapted for administration to a mammal, including a human being, to
17 treat or alleviate the conditions which were described above as treatable by
18 retinoids, or which are controlled by or responsive to the organism's native
19 retinoic acid. These formulations can also be co-administered with retinoids to
20 enhance or prolong the effects of medications containing retinoids or of the
21 organism's native retinoic acid.

22 The present invention also relates to a method of providing a compound
23 which is an inhibitor of the enzyme cytochrome P450RAI, wherein the method
24 of providing the cytochrome P450RAI inhibitory compound comprises:

25 identifying a compound that has activity as a retinoid in any of the art
26 recognized assays which demonstrate retinoid-like activity, the retinoid
27 compound having a formula such that it includes a benzoic acid, benzoic acid
28 ester, naphthoic acid, naphthoic acid ester or heteroaryl carboxylic acid or

1 ester moiety, with a partial structure of $-A(R_2)-(CH_2)_n-COOR_8$ where the
2 symbols are defined as in **Formulas 1** through **8**, and where **n** is 0, and
3 selecting a compound that is a homolog of the previously identified
4 retinoid compound where in the formula of the homolog **n** is 1 or 2, preferably
5 1. Said homolog, if it is not a previously known compound can be prepared
6 by homologation procedures well known to the synthetic organic chemist,
7 such as for example the well known *Arndt-Eistert* synthesis. Alternatively,
8 said homologs can be prepared by any of the applicable synthetic processes
9 illustrated below for the preparation of the novel compounds of **Formulas 1**
10 through **8** wherein the symbol **n** represents the integral 1 (one).

11 BRIEF DESCRIPTION OF THE DRAWING FIGURE

12 Figure 1 is a schematic representation of the P450RAI cell based assay
13 utilized to evaluate the ability of the compounds of the invention to inhibit the
14 Cytochrome P450RAI enzyme.

15 BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

16 P450RAI-1 Cell-Based Inhibitor Assay:

17 **Figure 1** shows a schematic diagram of the P450RAI-1 cell based
18 assay. P450RAI-1 stably transfected HeLa cells are maintained in 100
19 millimolar tissue culture dishes in Modified Eagle's Medium (MEM)
20 containing 10 % Fetal Bovine Serum (FBS) and 100 µg/ml hygromycin.
21 Exponentially growing cells are harvested by incubating in trypsin. Cells are
22 then washed with 1X Phosphate Buffered Saline (PBS) and plated in a 48-well
23 plate at 5×10^5 cells in 0.2 ml MEM medium containing 10 % FBS and 0.05
24 µCi [3H]-RA in the presence or absence of increasing concentrations of the test
25 compounds. The compounds are diluted in 100% DMSO and then added in
26 triplicate wells at either 10, 1 or 0.1 µM final concentration. As a positive
27 control for RA metabolism inhibition, cells are also incubated with
28 ketoconazole at 100, 10 and 1 µM. Cell are incubated for 3 hours at 37°C.

1 The retinoids are then extracted using the procedure of *Bligh et al.* (1959)
2 Canadian Journal of Biochemistry 37, 911-917, modified by using
3 methylenechloride instead of chloroform. The publication *Bligh et al.* (1959)
4 Canadian Journal of Biochemistry 37, 911-917 is specifically incorporated
5 herein by reference. The water soluble radioactivity is quantified using a β -
6 scintillation counter. IC_{50} values represent the concentration of inhibitor
7 required to inhibit all-*trans*-RA metabolism by 50 percent and are derived
8 manually from log-transformed data. The IC_{50} values obtained in this assay
9 for several novel compounds used in accordance with the invention are
10 disclosed in **Table 1** below. The IC_{50} values obtained in this assay for
11 several previously known compounds the cythochrome P450RAI inhibitory
12 activity of which has been discovered in accordance with the present
13 invention, are disclosed in **Table 1A** below.

14 Assays of Retinoid-like or Retinoid Antagonist and Inverse Agonist-like
15 Biological Activity

16 Assays described below measure the ability of a compound to bind to,
17 and/or activate various retinoid receptor subtypes. When in these assays a
18 compound binds to a given receptor subtype and activates the transcription of
19 a reporter gene through that subtype, then the compound is considered an
20 **agonist** of that receptor subtype. Conversely, a compound is considered an
21 **antagonist** of a given receptor subtype if in the below described co-transfection
22 assays the compound does not cause significant transcriptional activation of
23 the receptor regulated reporter gene, but nevertheless binds to the receptor
24 with a K_d value of less than approximately 1 micromolar. In the below
25 described assays the ability of the compounds to bind to RAR_α , RAR_β , RAR_γ ,
26 RXR_α , RXR_β and RXR_γ receptors, and the ability or inability of the
27 compounds to activate transcription of a reporter gene through these receptor
28 subtypes can be tested.

1 As far as specific assays are concerned, a **chimeric receptor**
2 **transactivation assay** which tests for agonist-like activity in the RAR α , RAR β ,
3 and RAR γ , receptor subtypes, and which is based on work published by
4 *Feigner P. L. and Holm M.* (1989) Focus, 112 is described in detail in United
5 States Patent No. 5,455,265. The specification of United States Patent No.
6 5,455,265 is hereby expressly incorporated by reference. The numeric results
7 obtained with several preferred novel compounds used in accordance with the
8 invention in this assay are shown below in **Table 1**. These data demonstrate
9 that generally speaking the compounds of **Formulas 1 through 8**, are not
10 agonists (or only weak agonists) of RAR retinoic receptors, and also that they
11 do not bind, or in some cases bind only weakly to RAR retinoid receptors.

12 A **holoreceptor transactivation assay** and a **ligand binding assay**
13 which measure the antagonist/agonist like activity of the compounds used in
14 accordance with the invention, or their ability to bind to the several retinoid
15 receptor subtypes, respectively, are described in published PCT Application
16 No. WO WO93/11755 (particularly on pages 30 - 33 and 37 - 41) published on
17 June 24, 1993, the specification of which is also incorporated herein by
18 reference. A detailed experimental procedure for holoreceptor
19 transactivations has been described by *Heyman et al.* Cell 68, 397 - 406,
20 (1992); *Allegretto et al.* J. Biol. Chem. 268, 26625 - 26633, and *Mangelsdorf*
21 *et al.* The Retinoids: Biology, Chemistry and Medicine, pp 319 - 349, Raven
22 Press Ltd., New York, which are expressly incorporated herein by reference.
23 The results obtained in this assay are expressed in EC₅₀ numbers, as they are
24 also in the **chimeric receptor transactivation assay**. The results of **ligand**
25 **binding assay** are expressed in K_d numbers. (See *Cheng et al.* Biochemical
26 Pharmacology Vol. 22 pp 3099-3108, expressly incorporated herein by
27 reference.)

28 The results if the ligand binding assay for several preferred novel

1 compounds used in accordance with the invention are included in Table 1. In
 2 the holoreceptor transactivation assay, tested for RXR $_{\alpha}$, RXR $_{\beta}$, and RXR $_{\gamma}$
 3 receptors, the novel compounds are, generally speaking, entirely devoid of
 4 activity, demonstrating that the novel compounds do not act as RXR agonists.

TABLE 1

Compound #	General Formula	Table # ¹	RAR EC ₅₀ /(EFFICACY)/K _d nM			P450RAI INHIBITION DATA
			α	β	γ	INTACT HELA IC ₅₀ μ M
110	2	3	NA 2058	74 (44) 409	262 (42) >10K	>10
112	2	3	NA 5853	335 (37) 704	NA 685	>10
3	4	5	280 (28) 145	4.8 (54) 0.8	9.8 (52) 158	3
114	2	3	NA >10K	NA >10K	NA >10K	>10
108	2	3	6.6 (15) 21K	283 (36) 547	141 (10) 13K	>10
116	2	3	NA 3269	WA 732	NA 886	>10
77	2	3	NA 2207	WA 225	NA 16	>10
78	2	3	NA >10K	NA >10K	NA >10K	>10

1	40	1	2	33 (207) 69	1.2 (126) 1.3	6.8 (140) 363	1.7
2	42	1	2	NA 15K	NA 3636	NA >10K	0.19
3	28	8	9	NA 21K	NA 4272	NA >10K	0.34
4	70	2	3	NA >10K	NA >10K	NA >10K	>10
5	69	2	3	313 (10) 469	12 (50) 133	52.6 (31) 501	>10
6	73	2	3	WA 486	22.5 (39) 26	91 (24) 351	>10
7	74	2	3	NA 11K	NA 14K	NA >10K	3.5
8	30	8	9	14	2.2	84	0.28
9	44	1	2	49 (138) 37	1.7 (100) 1.9	7.5 (116) 392	0.27
10	82	2	3	NA >10K	NA >10K	NA >10K	>10
11	81	2	3	NA 4210	490 (80) 846	183 (67) 1058	>10
12	89	2	3	268 (20) 3407	26 (50) 980	12 (46) 475	>10

1	90	2	3	NA >10K	NA >10K	NA >10K	0.95
2	94	2	3	NA >10K	NA >10K	NA >10K	>10
3	93	2	3	4821 (114) 3450	20 (39) 554	10 (55) 358	>10
4	5	8	9	NA 9148	11 (36) 2815	NA >10K	0.55
5	8	4	5	NA 10K	363 (96) 3781	NA 25K	0.4
6	86	2	3	NA >10K	NA >10K	NA >10K	1.4
7	85	2	3	976 (60) 1861	3.5 (77) 240	2.5 (65) 302	>10
8	98	2	3	NA	NA	NA	0.8
9	13	4	5	NA	3.2 (6.6)	116 (9)	3.1
10	10	8	9	57 (146)	0.3 (86)	6 (94)	0.7
11	36	8	9	13K	4896	492	0.033
12	38	8	9	10K	5317	2884	0.025

1	34	8	9	61.5	15	2.5	0.13
2	119	6	7	>10K	>10K	>10K	0.4
3	121	6	7	>10K	>100K	>100K	0.18
4	46	8	9	>10K	>10K	>10K	2.2
5	20	8	9				>10
6	18	4	5				1.1
7	32	8	9	27K	4225	13K	0.18
8	139	4	5				0.05
9	22	3	4				1.6
10	24	3	4				3
11	137	4	5				0.1
12	26	4	5				10
13	127	6	7				0.4
14	126	6	7				0.09
15	48	1	2				0.03

1	50	1	2				0.014
2	52	1	2				0.05
3	54	1	2				0.022
4	62	7	8				>10
5	56	8	9				0.13
6	134	6	7				5
7	58	1	2				0.18
8	60	1	2				1.6
9	143						0.8
10	145						0.2

11
12 ¹The "Table #" refers to Table 2 through 9 provided below where the
13 compound is identified with reference to a corresponding specific formula of
14 **Formulas 9 through 16.**

15
16 **Table 1A** below provides data similar to those provided in **Table 1**, for
17 certain previously known compounds which have been discovered in
18 accordance with the present invention to be useful as inhibitors of cytochrome
19 P450RAI. These compounds are shown by **Formula A** through **O** and have
20 **compounds numbers 201 through 247.**

21

TABLE 1A

Compound #	General Formula	RAR EC ₅₀ /(EFFICACY)/K _d nM			P450RAI INHIBITION DATA
		α	β	γ	INTACT HELA IC ₅₀ μ M
201	A	>10K 300 90	>10K (12) 1105	180 (24) 4391	0.52
202	A				0.6
203	C				0.62
204	C				0.7
205	C				1
206	C				1.8
207	D				1.2
208	D				1
209	E				1.7
210	A	89 (25) 10000	18 (122) 2891	15 (61) 10000	10
211	E				1.5
212	G				7
214	E				1.9
215	A				6.2
216	D				3.3
217	G				6.3
218	D				3.4
219	G				3.2
220	C				1
221	C				>10
222	F				>10

1	223	F				>10
2	224	C				5.5
3	225	C				>10
4	226	C				>10
5	227	C				1.3
6	228	C				6
7	229	G				1.6
8	230	D				5.1
9	231	K				4.1
10	232	D				4.2
11	233	M				1.3
12	234	M				4.7
13	235	E				7
14	236	E				5.5
15	237	J				6.8
16	238	A				7.2
17	240	B				3
18	241	N				5.5
19	242	I				5.8
20	243	L				7.4
21	244	G				5.1
22	245	H				3.3
23	246	J				3.1
24	247	O				10
25						

TOPICAL SKIN IRRITATION TESTS

As is known the topical retinoid all-trans-retinoic acid (ATRA) and oral retinoids such as 13-cis RA and etretinate are known to induce substantial skin irritation in humans. This irritation is a direct result of activation of the RAR nuclear receptors. Analysis of retinoid topical irritation is also a highly reproducible method of determining *in vivo* retinoid potency. The SKH1-*hrBR* or hairless mouse provides a convenient animal model of topical irritation, since retinoid-induced skin flaking and abrasion can be readily scored by eye (*Standeven et al.*, "Specific antagonist of retinoid toxicity in mice." Toxicol. Appl. Pharmacol., 138:169-175, (1996); *Thacher, et al.*, "Receptor specificity of retinoid-induced hyperplasia. Effect of RXR-selective agonists and correlation with topical irritation". J. Pharm. Exp. Ther., 282:528-534, (1997)). As is demonstrated below the topical application of P450RAI inhibitors in accordance with the present invention also causes an increase in the endogenous levels of ATRA that results in ATRA-induced irritation in skin of hairless mice. The attached data table discloses the retinoid-mimetic effects of some P450RAI inhibitor compounds in accordance with the present invention on the skin of hairless mice.

Methods

Female hairless mice (CrI:SKH1-*hrBR*), 5-7 weeks old, were obtained from Charles River Breeding Labs (Wilmington, MA). Animals were about 6 weeks old at the start of the experiments. Food (Purina Rodent Chow 5001) and reverse osmosis water were provided *ad libitum*. Mice were housed individually throughout the dosing period. In some experiments, mice that fit within a defined weight range, e.g., 21-25g, were selected from the available stock and then randomly assigned to the various treatment groups, using body weight as the randomization variable.

The compounds to be tested were dissolved in acetone for application

1 to the backs of the mice.

2 Mice were treated topically on the back in a volume of 4.0 ml/kg (0.07-
3 0.12ml) adjusted daily so as to deliver a fixed dose of test compound per g
4 body weight. Doses are disclosed as nmol/25g.

5 Unless indicated otherwise, mice were treated with retinoids once daily
6 on days 1 through 5 and observed on days 2, 3, 4, 5, 6, 7 and 8.

7 The mice were weighed daily and the dorsal skin was graded daily
8 using separate semi-quantitative scales to determine flaking and abrasion.
9 These flaking and abrasion scores were combined with weight change (if any)
10 to create a cutaneous toxicity score (Blackjack score).

11 Cutaneous Toxicity Score

12 A visual grading scale was used for characterizing topical irritation on a
13 daily basis. The grading scale used is as follows:

14

15	<u>Flaking</u>	<u>Abrasions</u>
16	0 = none	0 = none
17	1 = slight (small flakes, <50%	1 = slight (one or two abrasions with
18	coverage)	a light pink color)
19	2 = mild (small flakes, 50%	2 = mild (several abrasions with a
20	coverage)	pink color)
21	3 = moderate (small flakes, >50%	3 = moderate (one or two deep
22	coverage & large flakes, <25%	abrasions with red color, <25%
23	coverage)	coverage)
24	4 = severe (small flakes, >50%	4 = severe (multiple deep abrasions
25	coverage & large flakes, 25-50%	with red color, >25% coverage)
26	coverage)	
27	5 = very severe (large flakes, >50%	
28	coverage)	
29		

1 Topical Toxicity Score

2 The flaking and abrasion observations were combined with body
3 weight observations to calculate a single, semiquantitative topical or cutaneous
4 "toxicity score" as detailed below. The toxicity score (also known as
5 "blackjack score" since the theoretical maximum is 21) takes into account the
6 maximal severity, and the time of onset of skin flaking and abrasions and the
7 extent of weight between the first and last days of the experiment. Below are
8 listed the seven numerical components of the toxicity score and an explanation
9 of how those values are combined to calculate the toxicity score.

10 1. Flaking-Maximal Severity:

11 Highest flaking score attained during observation period.

12 2. Flaking-Day of Onset of grade 2 or worse:

13 0 - > 8 days

14 1 - day 8

15 2 - day 6 or 7

16 3 - day 4 or 5

17 4 - day 2 or 3

18 3. Flaking-Average Severity:

19 Flaking severity scores are summed and divided by the number
20 of observation days.

21 4. Abrasion-Maximal Severity:

22 Highest abrasion score attained during observation period.

23 5. Abrasion-Day of Onset of grade 2 or worse:

24 Same scale as (2) above.

25 6. Abrasion-Average Severity:

26 Abrasion severity scores are summed and divided by the number
27 of observation days.

28 7. Systemic Toxicity (weight loss):

- 1 0 - <1g
- 2 1 - 1 to 2g
- 3 2 - 2 to 4g
- 4 3 - 4 to 6g
- 5 4 - >6g or dead

6 Calculation of Composite Flaking Score

7 Flaking onset score (2) and average severity score (3) are summed and
8 divided by two. The quotient is added to the maximal severity score (1).
9 Composite flaking scores are calculated for each individual animal in a group,
10 averaged, and rounded to the nearest integer. Values can range from 0-9.

11 Calculation of Composite Abrasion Score

12 Abrasion onset score (5) and average severity score (6) are summed and
13 divided by two. The quotient is added to the maximal severity score (4).
14 Composite abrasion scores are calculated for each individual animal in a
15 group, averaged and rounded to the nearest integer. Values can range from 0-
16 8.

17 Calculation of Toxicity Score

18 Composite flaking score, composite abrasion score, and systemic
19 toxicity score are summed to give the "toxicity score." Toxicity scores are
20 calculated for each individual animal in a group, averaged, and rounded to the
21 nearest integer. Values can range from 0-21 and are expressed in **Table 1B**
22 below as the mean \pm SD of the values for a group.

23 Calculation of Percentage Change in Body Weight

24 The body weight at the time of the last weighing (day 8, 11, or 12) was
25 subtracted from the initial body weight. The difference was divided by the
26 initial body weight, multiplied by 100%, and rounded to the nearest integer.
27 Values were calculated for each individual animal and the mean and standard
28 deviation for each group are shown.

TABLE 1B

Compound No.	Cutaneous Toxicity Score (Blackjack Score)		
	100 nmole	300 nmole	1000 nmole
5	0		6±3
15	1 ± 1		5 ± 2
36	1 ± 1		11 ± 0
38	1 ± 1		10 ± 1
8	5 ± 2	8 ± 3	12 ± 1
22	0 ± 0	0 ± 0	1 ± 1
137	1 ± 1	1 ± 1	5 ± 2
48	1 ± 1	3 ± 1	7 ± 2
50	1 ± 0	3 ± 2	8 ± 2
58	0 ± 0	0 ± 0	0 ± 0
131	1 ± 1	0 ± 1	1 ± 1
127	0 ± 0	0 ± 0	0 ± 0
18	0 ± 0	5 ± 2	10 ± 2
247	1 ± 0	2 ± 1	6 ± 1

Modes of Administration

The compounds used in the methods of treatment of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and numerous other considerations. Thus, in the treatment of dermatoses, it will generally be preferred to administer the drug topically, though in certain cases such as treatment of severe cystic acne or psoriasis, oral administration may also be used. Any common topical formulation such

1 as a solution, suspension, gel, ointment, or salve and the like may be used.
2 Preparation of such topical formulations are well described in the art of
3 pharmaceutical formulations as exemplified, for example, by Remington's
4 Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton,
5 Pennsylvania. For topical application, the compounds could also be
6 administered as a powder or spray, particularly in aerosol form. If the drug is
7 to be administered systemically, it may be confectioned as a powder, pill, tablet or
8 the like or as a syrup or elixir suitable for oral administration. For intravenous
9 or intraperitoneal administration, the compound will be prepared as a solution
10 or suspension capable of being administered by injection. In certain cases, it
11 may be useful to formulate these compounds by injection. In certain cases, it
12 may be useful to formulate these compounds in suppository form or as
13 extended release formulation for deposit under the skin or intramuscular
14 injection.

15 Other medicaments can be added to such topical formulation for such
16 secondary purposes as treating skin dryness; providing protection against light;
17 other medications for treating dermatoses; medicaments for preventing
18 infection, reducing irritation, inflammation and the like.

19 Treatment of dermatoses or any other indications known or discovered
20 to be susceptible to treatment by retinoic acid-like compounds, or to control by
21 naturally occurring retinoic acid will be effected by administration of the
22 therapeutically effective dose of one or more compounds used in accordance
23 with the instant invention. A therapeutic concentration will be that
24 concentration which effects reduction of the particular condition, or retards its
25 expansion. In certain instances, the compound potentially may be used in
26 prophylactic manner to prevent onset of a particular condition.

27 A useful therapeutic or prophylactic concentration will vary from
28 condition to condition and in certain instances may vary with the severity of

1 the condition being treated and the patient's susceptibility to treatment.
2 Accordingly, no single concentration will be uniformly useful, but will require
3 modification depending on the particularities of the disease being treated.
4 Such concentrations can be arrived at through routine experimentation.
5 However, it is anticipated that in the treatment of, for example, acne, or similar
6 dermatoses, that a formulation containing between 0.01 and 1.0 milligrams per
7 milliliter of formulation will constitute a therapeutically effective
8 concentration for total application. If administered systemically, an amount
9 between 0.01 and 5 mg per kg of body weight per day would be expected to
10 effect a therapeutic result in the treatment of many diseases for which these
11 compounds are useful.

12 In some applications pharmaceutical formulations containing the CP-
13 450RAI inhibitory compounds may be co-administered with formulations
14 containing retinoids. In such cases the dose of the cytochrome P450RAI
15 inhibitors compounds is in the range of 0.01 and 5 mg per kg body weight per
16 day.

17 GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY

18 Definitions

19 The term alkyl refers to and covers any and all groups which are known
20 as normal alkyl and branched-chain alkyl. Unless specified otherwise, lower
21 alkyl means the above-defined broad definition of alkyl groups having 1 to 6
22 carbons in case of normal lower alkyl, and 3 to 6 carbons for lower branch
23 chained alkyl groups. A pharmaceutically acceptable salt may be prepared for
24 any compound used in accordance with the invention having a functionality
25 capable of forming a salt, for example an acid functionality. A
26 pharmaceutically acceptable salt is any salt which retains the activity of the
27 parent compound and does not impart any deleterious or untoward effect on
28 the subject to which it is administered and in the context in which it is

1 administered.

2 Pharmaceutically acceptable salts may be derived from organic or
3 inorganic bases. The salt may be a mono or polyvalent ion. Of particular
4 interest are the inorganic ions, sodium, potassium, calcium, and magnesium.
5 Organic salts may be made with amines, particularly ammonium salts such as
6 mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed
7 with caffeine, tromethamine and similar molecules. Where there is a nitrogen
8 sufficiently basic as to be capable of forming acid addition salts, such may be
9 formed with any inorganic or organic acids or alkylating agent such as methyl
10 iodide. Preferred salts are those formed with inorganic acids such as
11 hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of
12 simple organic acids such as mono-, di- or tri- acid may also be used.

13 Some compounds used in accordance with the present invention may
14 have *trans* and *cis* (E and Z) isomers. Unless specific orientation of
15 substituents relative to a double bond or a ring is indicated in the name of the
16 respective compound, and/or by specifically showing in the structural formula
17 the orientation of the substituents relative to the double bond or ring the
18 invention covers *trans* as well as *cis* isomers.

19 Some of the compounds used in accordance with the present invention
20 may contain one or more chiral centers and therefore may exist in
21 enantiomeric and diastereomeric forms. The scope of the present invention is
22 intended to cover all isomers *per se*, as well as mixtures of *cis* and *trans*
23 isomers, mixtures of diastereomers and racemic mixtures of enantiomers
24 (optical isomers) as well. A bond drawn with a wavy line indicates that the
25 carbon to which the bond is attached can be in any of the applicable possible
26 configurations.

27 General Synthetic Methodology

28 The novel compounds used in accordance with the invention are

1 encompassed by the general Formulas 1 through 8 provided above. The
2 previously known compounds the cytochrome P450RAI activity of which has
3 been discovered in accordance with the present invention are identified below,
4 and references are provided which enable their preparation by one of
5 ordinary skill in the art of synthetic organic chemistry. In each of these
6 formulas a linker or tethering group designated Z covalently connects an
7 aromatic or heteroaromatic moiety designated $A(R_2)-(CH_2)_n-COOR_8$ and
8 another cyclic moiety which in accordance with these formulas is a substituted
9 phenyl, substituted tetrahydronaphthalene, substituted chroman, thiochroman,
10 tetrahydroquinoline or tetrahydroisoquinoline moiety. Generally speaking a
11 compound such as $X_4-A(R_2)-(CH_2)_n-COOR_8$ is commercially available, or
12 can be made in accordance with the chemical literature, or with such
13 modification of known chemical processes which are within the skill of the
14 practicing organic chemist. The group X_4 represents a reactive group, which
15 is suitable for coupling the $X_4-A(R_2)-(CH_2)_n-COOR_8$ compound to a
16 derivative of the substituted phenyl, substituted tetrahydronaphthalene,
17 substituted chroman, thiochroman, tetrahydroquinoline or
18 tetrahydroisoquinoline moiety so that as a result of the coupling the linker or
19 tether moiety Z is formed. In many instances the group X_4 is a leaving group
20 such as halogen, or trifluoromethanesulfonyloxy, or a group capable of
21 participating in a *Wittig* or *Horner Emmons* reaction. In some instances the
22 group X_4 is an ethynyl group capable of undergoing a coupling reaction with a
23 leaving group (such as a halogen or a trifluoromethanesulfonyloxy group)
24 attached to the substituted phenyl, substituted tetrahydronaphthalene,
25 substituted chroman, thiochroman, tetrahydroquinoline or
26 tetrahydroisoquinoline moiety. The group X_4 can also represent an OH or an
27 NH_2 group that forms an ester (COO) or amide (CONH) linker, respectively,
28 when reacted with an activated carboxyl derivative of the substituted phenyl,

1 substituted tetrahydronaphthalene, substituted chroman, thiochroman,
2 tetrahydroquinoline or tetrahydroisoquinoline moiety. Examples for the
3 compounds of formula $X_4-A(R_2)-(CH_2)_n-COOR_8$ are provided in the specific
4 examples below. Further examples where the X_4 group is halogen are ethyl
5 4-iodobenzoate, ethyl 6-iodonicotinate, ethyl 5-iodofuran-3-carboxylate, ethyl
6 5-iodothiophen-3-carboxylate, ethyl 5-iodofuran-2-carboxylate, ethyl 5-
7 iodothiophen-2-carboxylate, and analogous halogenated derivatives of the
8 respective pyridazine, pyrazine and other heteroaryl carboxylic acid esters.
9 The analogous aryl and heteroaryl hydroxyl compounds and amines,
10 wherein the halogen of the above-listed compounds is replaced by OH or NH_2
11 respectively, also serve as additional examples for the reagents of the formula
12 $X_4-A(R_2)-(CH_2)_n-COOR_8$. In these examples X_4 is OH or NH_2 , respectively.

13 Still further in accordance with the general synthetic methodology to
14 provide the compounds of **Formulas 1 through 8** a derivative of the
15 substituted phenyl, substituted tetrahydronaphthalene, substituted chroman,
16 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety is
17 synthesized first, having a covalently attached X_5 group. The X_5 group reacts
18 with the X_4 group of the reagent $X_4-A(R_2)-(CH_2)_n-COOR_8$ to form the linker
19 designated **Z** in **Formulas 1 through 8**. The X_5 group is one that is capable of
20 participating in a catalyzed coupling reaction, (such as an ethynyl group when
21 X_4 is a leaving group), or a leaving group (such as halogen or
22 trifluoromethanesulfonyloxy when X_4 is an ethynyl group), or an activated
23 carboxylic acid function (when X_4 is OH or NH_2). The X_5 group can also be
24 an OH, SH or NH_2 group when the X_4 group is an activated carboxylic acid
25 function. Specific examples for substituted phenyl, substituted
26 tetrahydronaphthalene, substituted chroman, thiochroman, tetrahydroquinoline
27 or tetrahydroisoquinoline intermediates having an X_5 functionality are
28 provided below, and are also available in the chemical scientific and patent

1 literature. Generally speaking, for reagents and reactions covalently joining a
2 substituted tetrahydronaphthalene, substituted chroman, thiochroman, or
3 tetrahydroquinoline intermediate with a substituted aryl or heteroaryl group,
4 such as $X_4-A(R_2)-(CH_2)_n-COOR_8$, to form a compound including the linker
5 designated **Z**, reference is made to United States Patent Nos. 5,648,503;
6 5,723,666 and 5,952,345 the specification of each of which are expressly
7 incorporated herein by reference.

8 The substituted phenyl, tetrahydronaphthalene, chroman, thiochroman,
9 tetrahydroquinoline or tetrahydroisoquinoline moiety of the novel compounds
10 used in accordance with the invention are derivatized in a manner to include
11 the specific substituents (such as for example the cycloalkyl substituents)
12 encompassed within the scope of the invention, either before or after the -
13 $A(R_2)-(CH_2)_n-COOR_8$ moiety has been attached and the linker **Z** has formed,
14 as illustrated by the below described specific examples.

15 The $-(CH_2)_n-COOR_8$ moiety of the compounds of **Formulas 1** through **8** can
16 be modified in order to obtain still further novel compounds. One such
17 modification is saponification of compounds where the R_8 group is an alkyl or
18 $-CH_2O(C_{1-6}\text{-alkyl})$ group. Another modification is esterification of the
19 carboxylic acid function when the R_8 group is H or a cation. Such
20 saponification and esterification reactions are well known in the art and within
21 the skill of the practicing organic chemist. Still another modification of the
22 compounds used in accordance with the invention (or of the intermediates X_4-
23 $A(R_2)-(CH_2)_n-COOR_8$, or of precursors to these intermediates) is the
24 homologation of the $(CH_2)_n$ group. The latter can be accomplished, for
25 example, by the well known *Arndt-Eistert* method of homologation, or other
26 known methods of homologation.

27 The previously known compounds which have been discovered to be
28 inhibitors of cytochrome P450RAI and which are used in accordance with

1 the present invention are made, generally speaking, pursuant to the teachings
2 of a patent or publication which is identified in connection with each of the
3 known compounds. These patents or publications are incorporated by
4 reference in the present specification.

5 The synthetic procedure of homologation that may be utilized for
6 providing a compound having the partial structure of $-A(R_2)-(CH_2)_n-COOR_8$
7 where n is 1, or 2 (one or two), preferably 1 (one), can be one of the several
8 known procedures of homologation of carboxylic acids or esters, such as the
9 *Arndt-Eistert* procedure that is described *inter alia* in March, Advanced
10 Organic Chemistry: Reactions, Mechanisms, and Structure, pages 809-810,
11 McGraw-Hill Publishers, 1968, incorporated herein by reference. Alternatively
12 the homologs of the partial structure of $-A(R_2)-(CH_2)_n-COOR_8$ are
13 synthesized in accordance with the synthetic schemes disclosed herein in
14 connection with the preparation of the novel compounds.

15 SPECIFIC EMBODIMENTS

16 With reference to the symbol **A** in **Formulas 1** through **8**, the preferred
17 novel compounds used in accordance with the present invention are those
18 where **A** is phenyl, naphthyl, pyridyl, thienyl or furyl. Even more preferred
19 are compounds where **A** is phenyl. As far as substitutions on the **A** (phenyl)
20 and **A** (pyridyl) groups are concerned, compounds are preferred where the
21 phenyl group is 1,4 (*para*) substituted and where the pyridine ring is 2,5
22 substituted. (Substitution in the 2,5 positions in the "pyridine" nomenclature
23 corresponds to substitution in the 6-position in the "nicotinic acid"
24 nomenclature.) In the presently preferred novel compounds used in
25 accordance with the invention either there is no R_2 substituent on the **A** group,
26 or the R_2 substituent is preferably a fluoro group that is preferably located on
27 the aromatic carbon adjacent (*ortho*) to the carbon bearing the $-(CH_2)_n-$
28 $COOR_8$ group.

1 As far as the $-(CH_2)_n-COOR_8$ is concerned the use of novel
2 compounds is preferred where n is 0, 1 or 2, and even more preferred where n
3 is 1. In **Formulas 5 and 8** only compounds where n is 1 or 2 are preferred,
4 with $n=1$ being most preferred. For the R_8 group H, lower alkyl of 1 to 3
5 carbons, and $-CH_2O(C_{1-6}\text{-alkyl})$ groups are preferred, as well as the
6 pharmaceutically acceptable salts of the free acids when R_8 is H. Among the
7 lower alkyl and $-CH_2O(C_{1-6}\text{-alkyl})$ groups ethyl and OCH_2CH_3 , respectively,
8 are presently most preferred.

9 The linker group Z in all of the novel compounds used in accordance
10 with the invention is preferably ethynyl
11 $(-C\equiv C-)$, ester $(CO-O)$, ethenyl, $(-CR_1=CR_1-)$ or amide $(CONR_1)$. Among
12 these the ethynyl $(-C\equiv C-)$ and ester $(CO-O)$ linkers are most preferred.
13 Moreover, preferably the linker Z is attached to the 6 position in **Formula 1**,
14 to the 4 position in **Formula 2**, to the 6 position in **Formula 3**, to the 6
15 position in **Formula 4**, to the 4 position in **Formula 5**, to the 4 position in
16 **Formula 6**, to the 6 position in **Formula 7**, and to the 6 position in **Formula**
17 **8**. These positions are indicated by arabic numerals in **Formulas 1 through 8**.

18 The R_1 group substituting the non-aromatic rings in **Formulas 1, 3, 4, 7**
19 and **8** is preferably alkyl, more preferably alkyl of 1 to 3 carbons, and most
20 preferably methyl. The R_1 group substituting the cyclopropane ring in
21 **Formulas 1, 2, 3 and 7** is preferably non-existent (p is 0), or is alkyl of 1 to 3
22 carbons, even more preferably methyl.

23 The X group in **Formulas 1 and 5** is preferably O, and in **Formula 2** X
24 is preferably O or NR.

25 The X_1 group in **Formula 4** is preferably 1-imidazolyl, substituted 1-
26 imidazolyl, or NRR_6 , where R_6 is preferably cyclopropyl or branched-chain
27 alkyl. The X_2 group in **Formula 6** is preferably 1-imidazolyl or substituted
28 1-imidazolyl.

1 The **X₃** group in **Formula 8** is preferably O or C=O.

2 The **Y** group is preferably H, lower alkyl of 1 to 3 carbons, cycloalkyl,
3 lower alkyl substituted cycloalkyl, or halogen. Among these, H, Cl, and
4 cyclopropyl are most preferred.

5 The **Y₁** group of **Formula 8** is preferably H, lower alkyl of 1 to 3
6 carbons, cycloalkyl, or lower alkyl substituted cycloalkyl. Among these H,
7 ethyl and cyclopropyl are presently most preferred.

8 The most preferred novel compounds used in accordance with the
9 invention are disclosed in **Tables 2** through **9** with reference to **Formulas 9**
10 through **16**. The compounds specifically shown in **Tables 2** through **9** are
11 carboxylic acids, but it should be understood that the use of the corresponding
12 C₁₋₃alkyl esters, methoxymethyl (OCH₂CH₃) esters and of pharmaceutically
13 acceptable salts of the acids shown in these tables is also highly preferred.

14 It should also be apparent that the preferred compounds shown in **Table**
15 **2** with reference to the more specific **Formula 9** are within the scope of
16 **Formula 1**.

17 Similarly, the preferred compounds shown in **Table 3** with reference to
18 the more specific **Formula 10** are within the scope of **Formula 2**;

19 the preferred compounds shown in **Table 4** with reference to the more
20 specific **Formula 11** are within the scope of **Formula 3**;

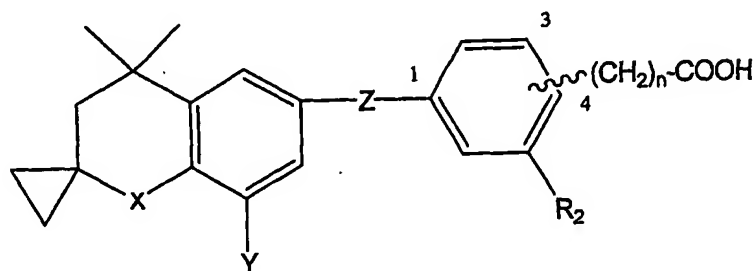
21 the preferred compounds shown in **Table 5** with reference to the more
22 specific **Formula 12** are within the scope of **Formula 4**;

23 the preferred compounds shown in **Table 6** with reference to the more
24 specific **Formula 13** are within the scope of **Formula 5**;

25 the preferred compounds shown in **Table 7** with reference to the more
26 specific **Formula 14** are within the scope of **Formula 6**;

27 the preferred compounds shown in **Table 8** with reference to the more
28 specific **Formula 15** are within the scope of **Formula 7**, and

the preferred compounds shown in Table 9 with reference to the more specific Formula 16 are within the scope of Formula 8.

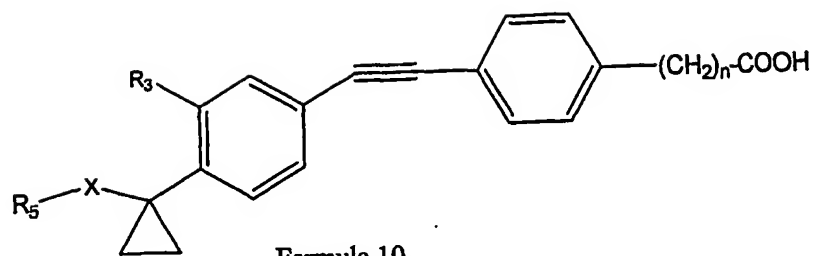


Formula 9

TABLE 2

Compound No.	X	Y	Z	R ₂	n	Position of (CH ₂) _n COOH
40	O	H	-C≡C-	H	0	4
42	O	H	-C≡C-	H	1	4
44	O	H	-C≡C-	F	0	4
48	O	cyclopropyl	-C≡C-	H	1	4
50	O	cyclopropyl	-C≡C-	F	1	4
52	O	cyclopropyl	-C≡C-	H	0	4
54	O	cyclopropyl	-C≡C-	F	0	4
58	O	cyclopropyl	-CO-O-	H	1	4
60	O	cyclopropyl	-CO-O-	H	1	3
66	CH ₃ N	H	-C≡C-	H	0	4

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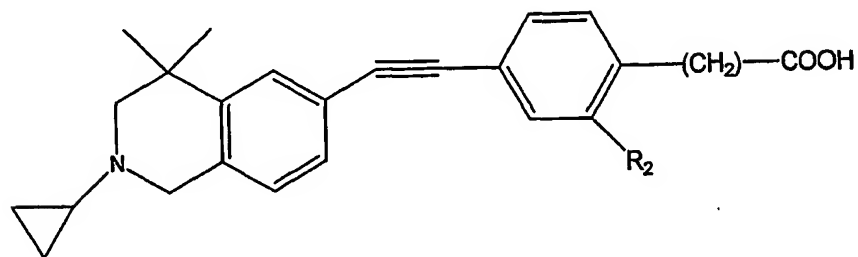
Formula 10

TABLE 3

Compound No.	R_5	X	R_3	n
110	n-propyl	(n-propyl)N	H	0
112	benzyl	NH	H	0
114	benzyl	(n-benzyl)N	H	0
108	n-propyl	NH	H	0
116	benzyl	methylN	H	0
77	benzyl	O	H	0
78	benzyl	O	H	1
70	methyl	O	H	1
69	methyl	O	H	0
73	isopropyl	O	H	0
74	isopropyl	O	H	1
82	benzyl	O	methyl	1
81	benzyl	O	methyl	0
89	$(CH_3)_3C-CH_2-$	O	methyl	0
90	$(CH_3)_3C-CH_2-$	O	methyl	1
94	benzyl	O	ethyl	1
93	benzyl	O	ethyl	0

50

1	86	isopropyl	O	methyl	1
2	85	isopropyl	O	methyl	0
3	105	ethyl	O	<i>t</i> -butyl	0
4	106	ethyl	O	<i>t</i> -butyl	1
5	98	isopropyl	O	ethyl	1

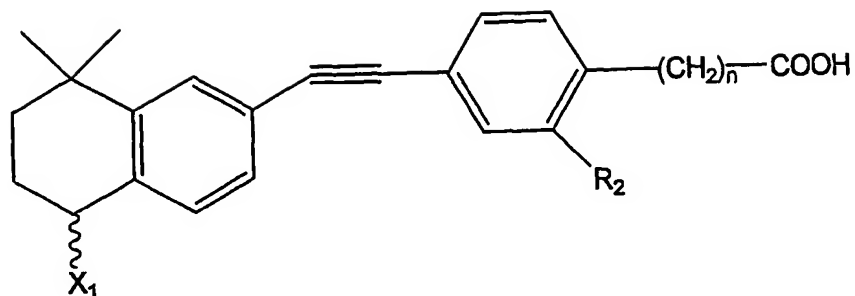


Formula 11

TABLE 4

22	Compound No.	R ₂
23	22	F
24	24	H

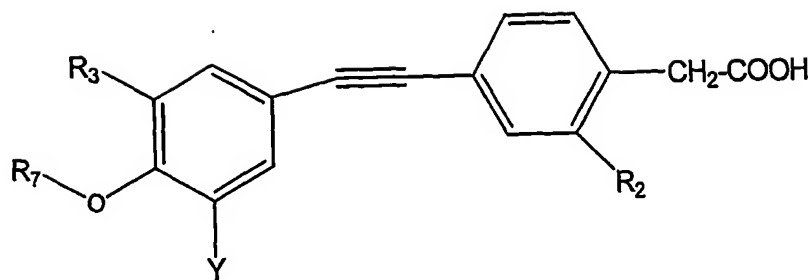
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Formula 12

TABLE 5

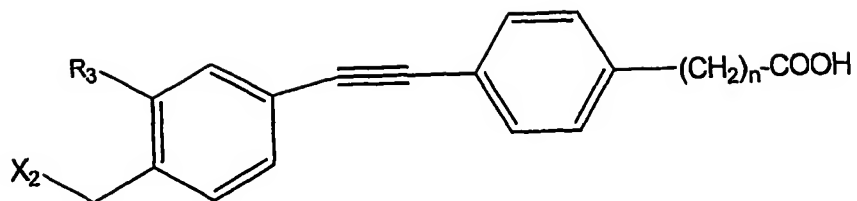
Compound No.	X_1	R_2	n
3	methyl,cyclopropyl-N	H	0
8	methyl,cyclopropyl-N	H	1
13	methyl,cyclopropyl-N	F	0
18	methyl,cyclopropyl-N	F	1
139	1-imidazolyl	H	0
137	1-imidazolyl	H	1
26	methyl,isopropyl-N	H	0



Formula 13

TABLE 6

Compound No.	R_2	R_7	Y	R_3
143	H	methyl	<i>t</i> -butyl	<i>t</i> -butyl
145	F	methyl	<i>t</i> -butyl	<i>t</i> -butyl



Formula 14

TABLE 7

Compound No.	X_2	R_3	n
119	1-imidazolyl	methyl	0
121	1-imidazolyl	methyl	1
127	1-imidazolyl	iso-propyl	1
126	1-imidazolyl	iso-propyl	0
134	ethyl,cyclopropyl-N	iso-propyl	0
130	ethyl,cyclopropyl-N	methyl	0
131	ethyl,cyclopropyl-N	methyl	1
141	(1-methyl)cyclopropyl-oxy	iso-propyl	1

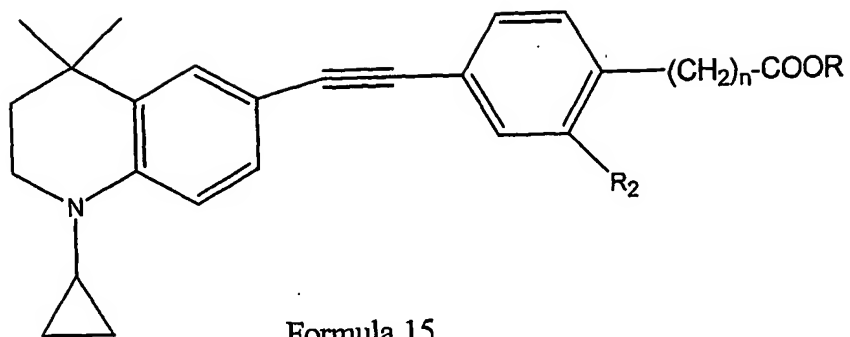
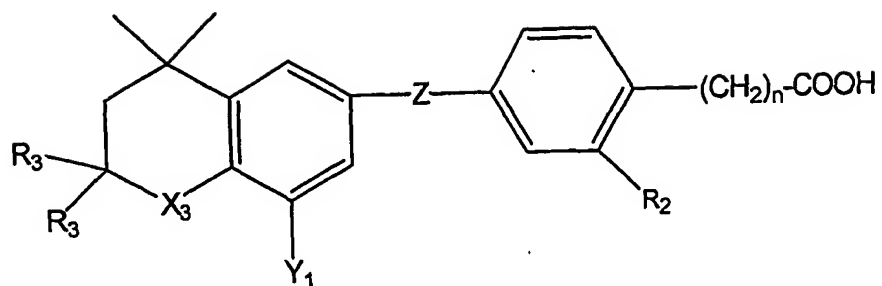


TABLE 8

Compound No.	R	R ₂	n
62	H	H	0
63	Me	H	1



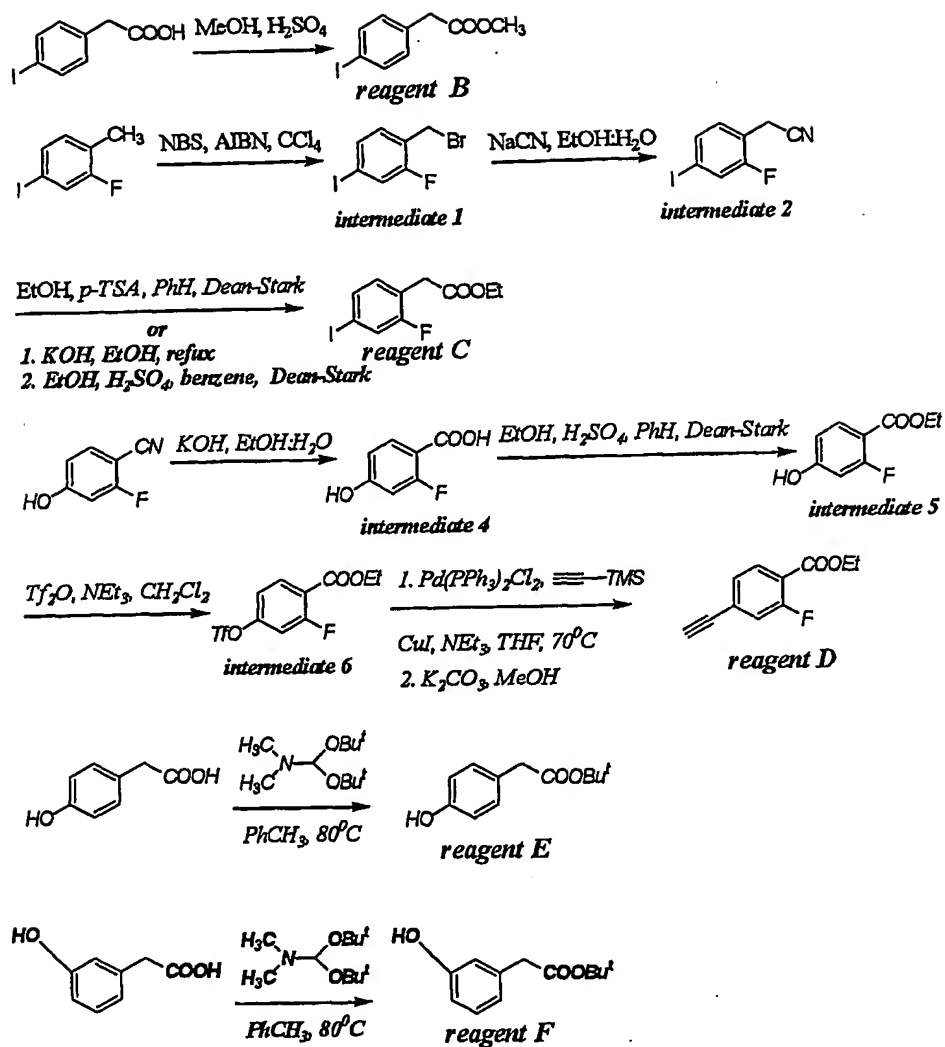
Formula 16

TABLE 9

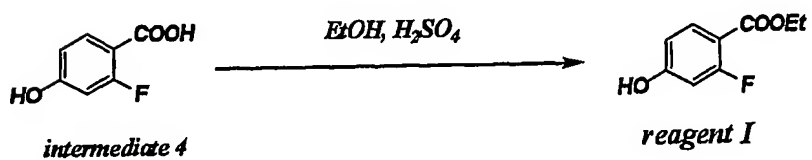
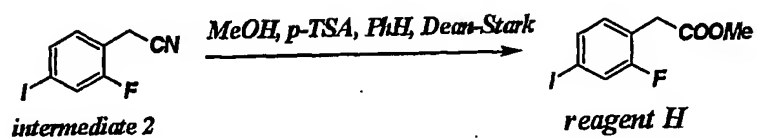
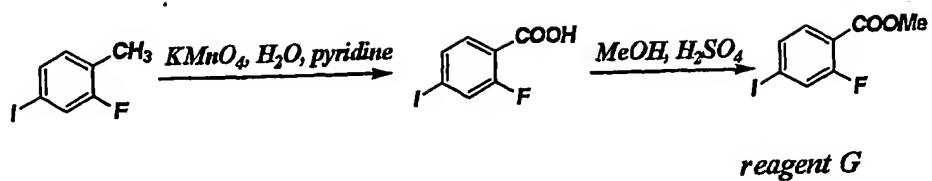
Compound No.	X ₃	Y ₁	R ₃	Z	R ₂	n
28	O	H	methyl	-C≡C-	H	1
30	O	H	methyl	-C≡C-	F	0
5	CO	H	H	-C≡C-	H	1
10	CO	H	H	-C≡C-	F	0
36	O	cyclopropyl	methyl	-C≡C-	H	1
38	O	cyclopropyl	methyl	-C≡C-	F	1
46	O	H	methyl	-CO-O-	H	1
20	CO	H	H	-CO-O-	H	1
32	O	H	methyl	-C≡C-	F	1
56	O	ethyl	methyl	-C≡C-	H	1
34	O	cyclopropyl	methyl	-C≡C-	H	0
15	CO	H	H	-C≡C-	F	1

1 The compounds used in accordance with the invention can be
2 synthesized by applying the general synthetic methodology described above,
3 and by such modifications of the hereinafter described specific synthetic routes
4 which will become readily apparent to the practicing synthetic organic chemist
5 in light of this disclosure and in view of general knowledge available in the
6 art. The hereinafter disclosed specific reaction schemes are directed to the
7 synthesis of exemplary and preferred compounds used in accordance with the
8 invention. Whereas each of the specific and exemplary synthetic routes shown
9 in these schemes may describe specific compounds only within the scope of
10 one or two of the general **Formulas 1 through 8**, the synthetic processes and
11 methods used therein are adaptable within the skill of the practicing organic
12 chemist and can be used with such adaptation for the synthesis of compounds
13 used in accordance with the invention which are not specifically described
14 herein as examples.

15 **Reaction Scheme 1** discloses a presently preferred synthetic route to
16 certain intermediates or reagents having the general formula $X_4-A(R_2)-CH_2)_n-$
17 $COOR_g$, where the symbol **A** represents a di-, or tri-substituted phenyl
18 moiety. These intermediates are utilized in the synthesis of the novel
19 compounds used in accordance with the invention.



REACTION SCHEME I



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REACTION SCHEME 1 CONTINUED

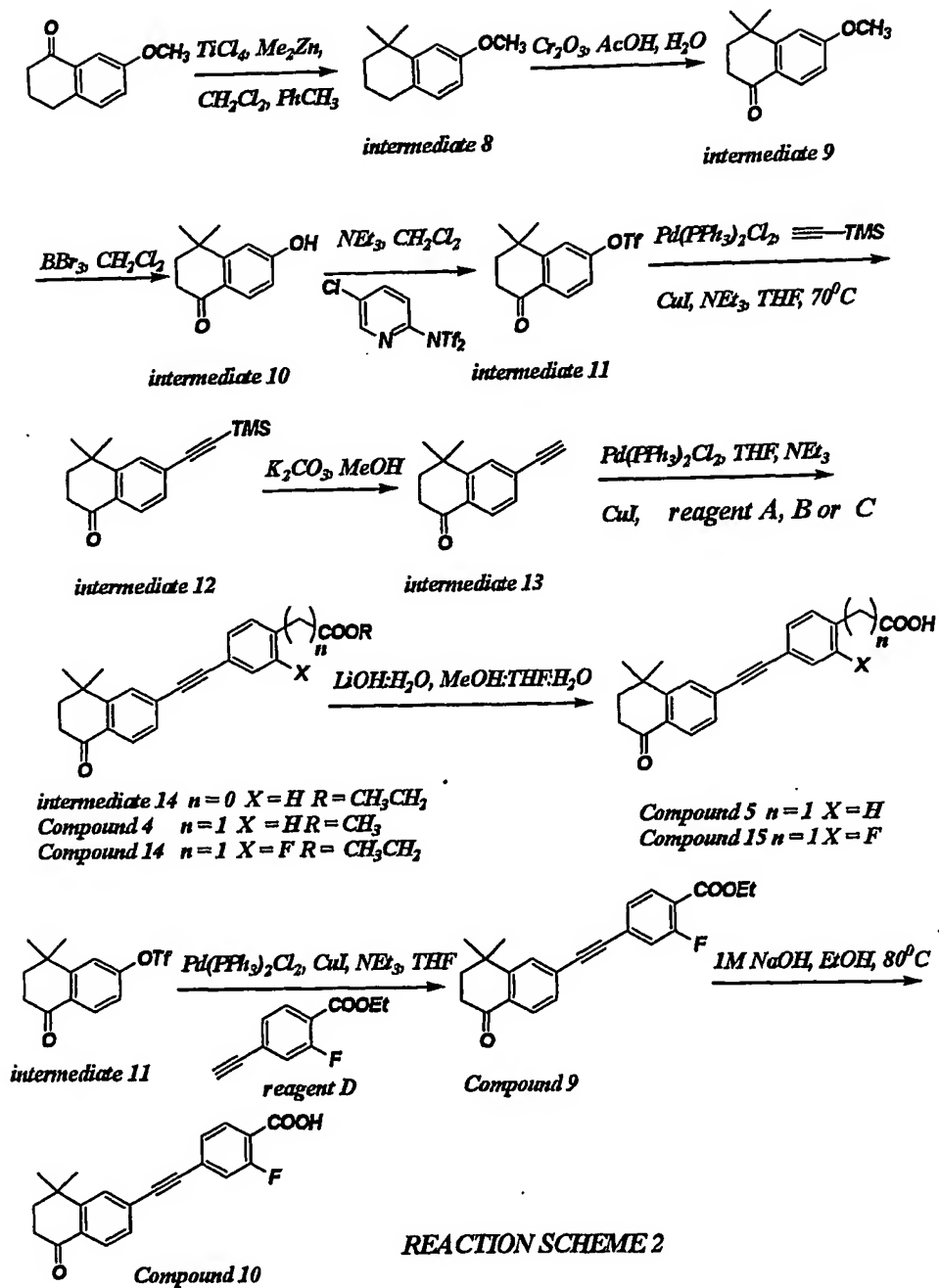
1 **Reaction Scheme 2** discloses presently preferred synthetic routes to
2 obtain exemplary and preferred novel tetrahydronaphthalenone compounds
3 within the scope of **Formula 8** where the the symbol X_3 represents a C=O
4 group, **Z** represents an ethynyl moiety or a -COO- (ester) function, and **A** is a
5 substituted phenyl moiety.

6 **Reaction Scheme 3** discloses presently preferred synthetic routes to
7 obtain exemplary and preferred novel tetrahydronaphthalene compounds
8 within the scope of **Formula 4** where X_1 represents a dialkyl substituted
9 nitrogen, **Z** is an ethynyl moiety and **A** is a substituted phenyl moiety.

10 **Reaction Scheme 4** discloses presently preferred synthetic routes to
11 obtain exemplary and preferred novel isoquinoline compounds within the
12 scope of **Formula 3** where the symbol **Y** represents hydrogen, **Z** is an
13 ethynyl moiety and **A** is a substituted phenyl moiety.

14 **Reaction Scheme 5** discloses presently preferred synthetic routes to
15 obtain exemplary and preferred novel chroman compounds within the scope of
16 **Formula 8** where the symbol Y_1 represents hydrogen, **Z** is an ethynyl moiety
17 or an ester (COO) function, and **A** is a substituted phenyl moiety.

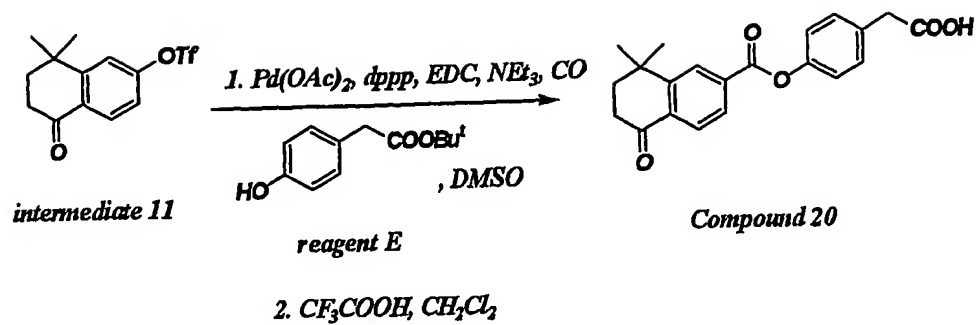
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**REACTION SCHEME 2 CONTINUED**

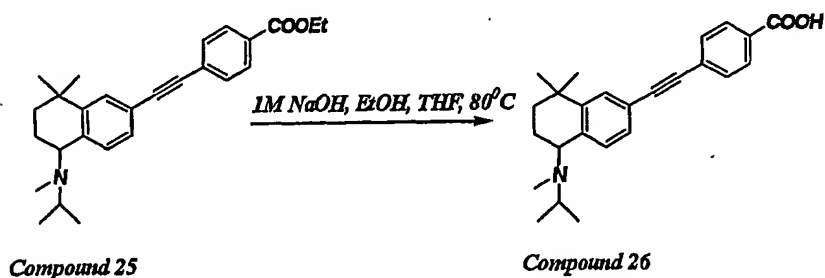
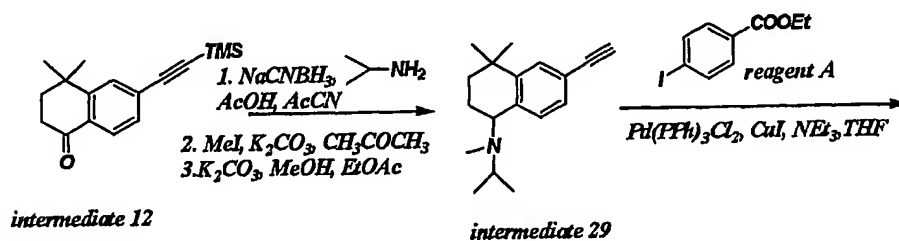
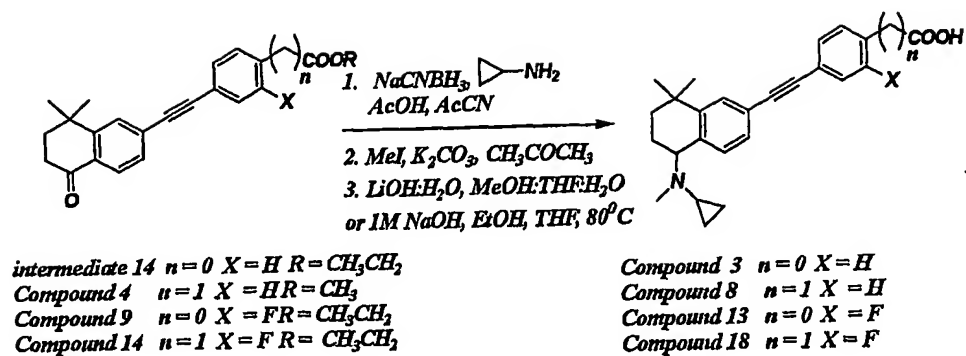
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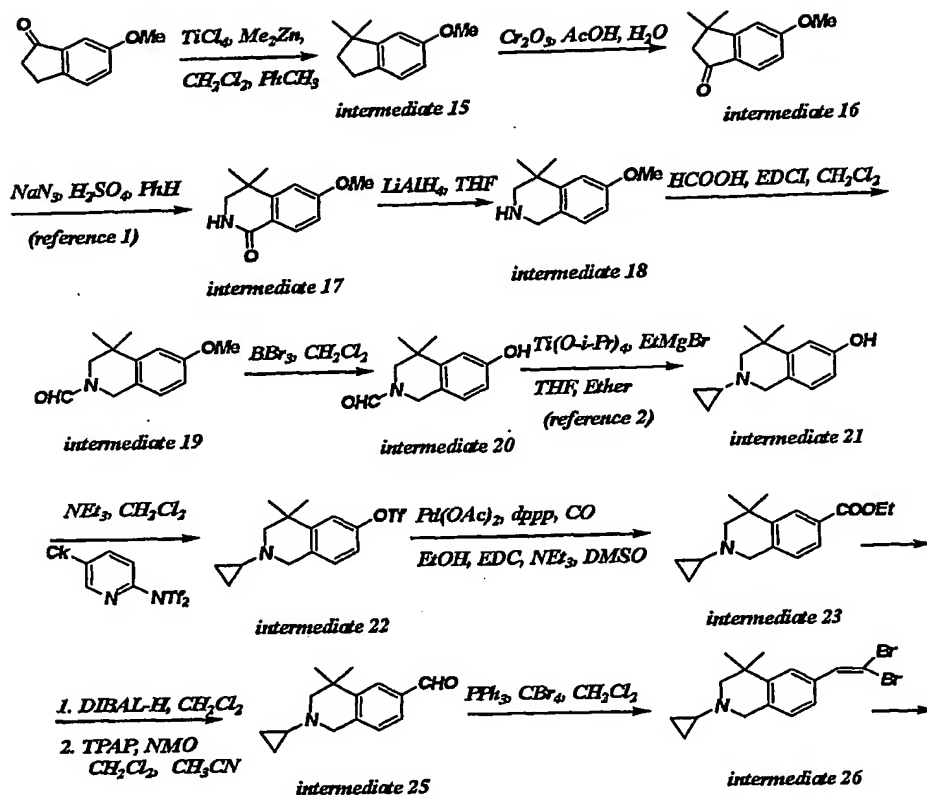
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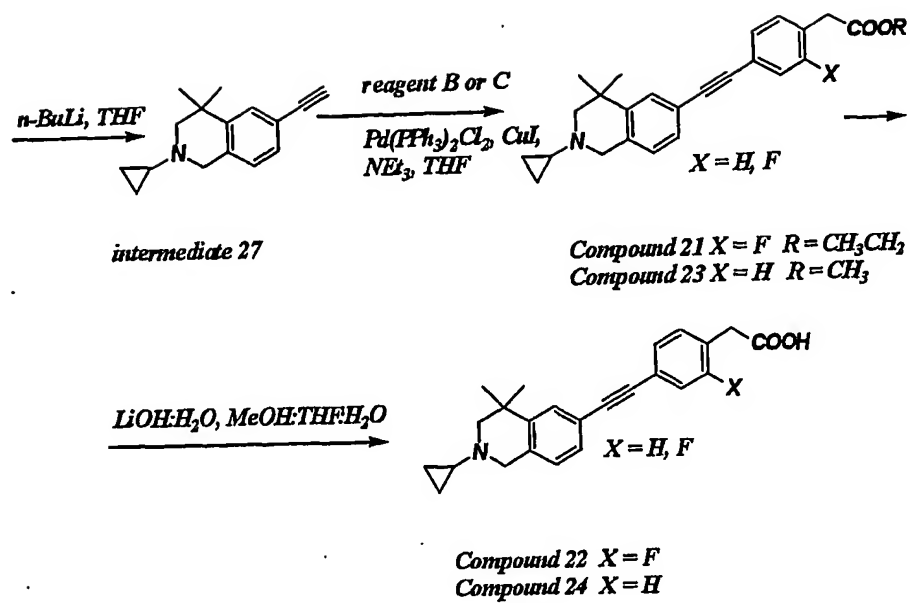
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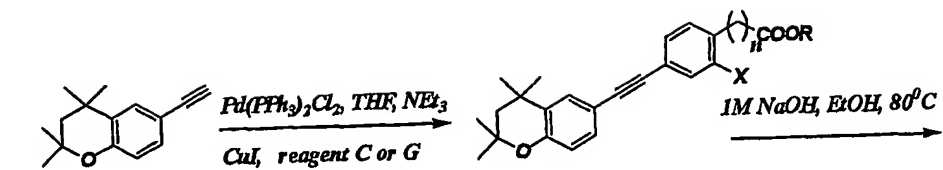
REACTION SCHEME 3





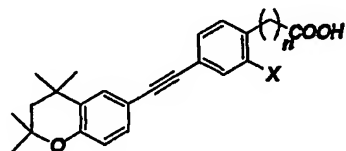
REACTION SCHEME 4 CONTINUED

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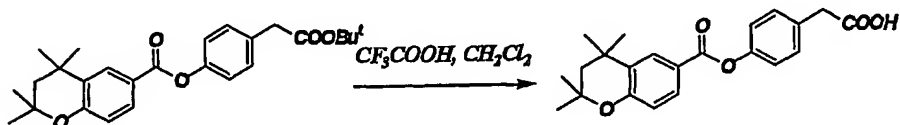
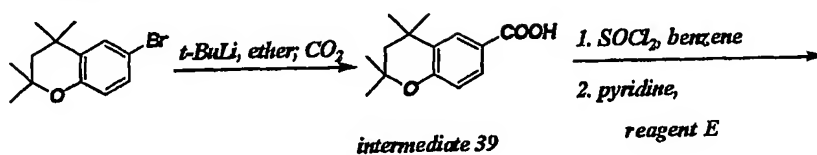


U. S. Patent Nos. 5,045,551 and 5,616,597

Compound 29 $X = \text{F } n = 0 \text{ } R = \text{CH}_3$
 Compound 31 $X = \text{F } n = 1 \text{ } R = \text{CH}_2\text{CH}_3$



Compound 30 $X = \text{F } n = 0$
 Compound 32 $X = \text{F } n = 1$



Compound 45

Compound 46

REACTION SCHEME 5

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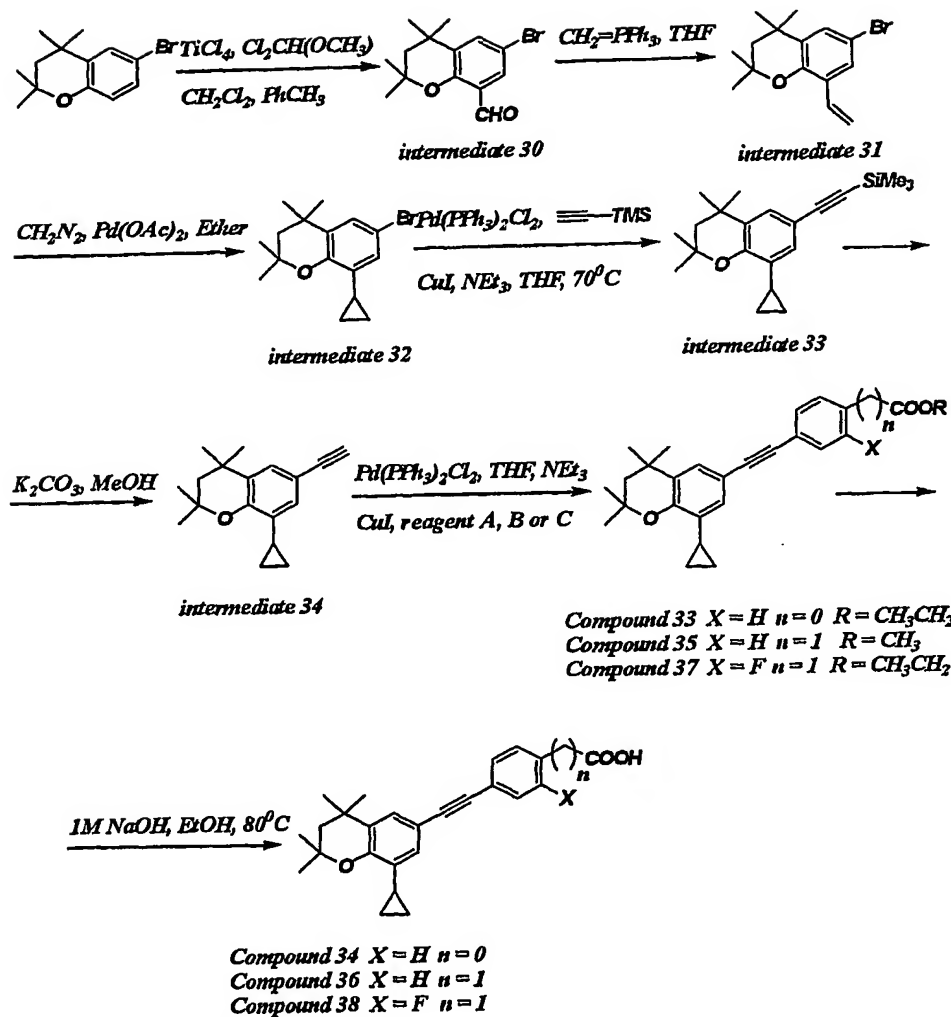
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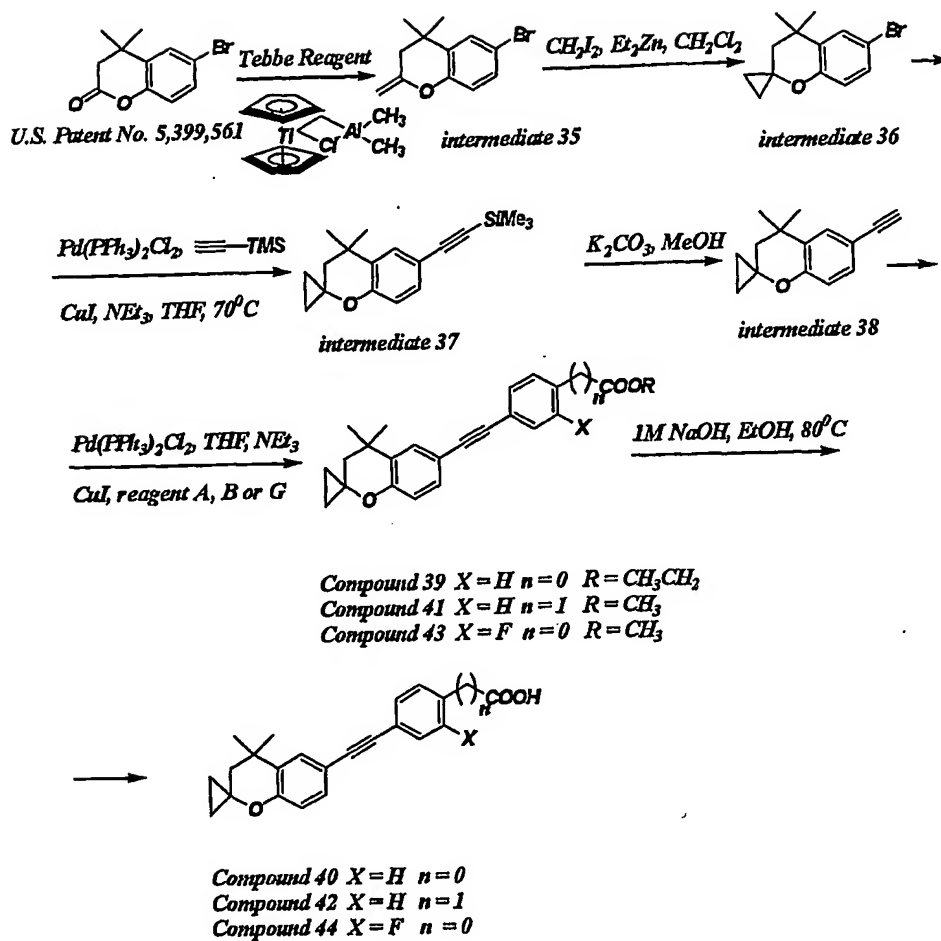
1 **Reaction Scheme 6** discloses presently preferred synthetic routes to
2 obtain other exemplary and preferred novel chroman compounds within the
3 scope of **Formula 8** where the symbol Y_1 represents a cyclopropyl group, **Z**
4 is an ethynyl moiety and **A** is a substituted phenyl moiety.

5 **Reaction Scheme 7** discloses presently preferred synthetic routes to
6 obtain exemplary and preferred novel chroman compounds within the scope of
7 **Formula 1** where the symbol **X** represents oxygen (O), **Y** represents
8 hydrogen, **Z** is an ethynyl moiety and **A** is a substituted phenyl moiety.

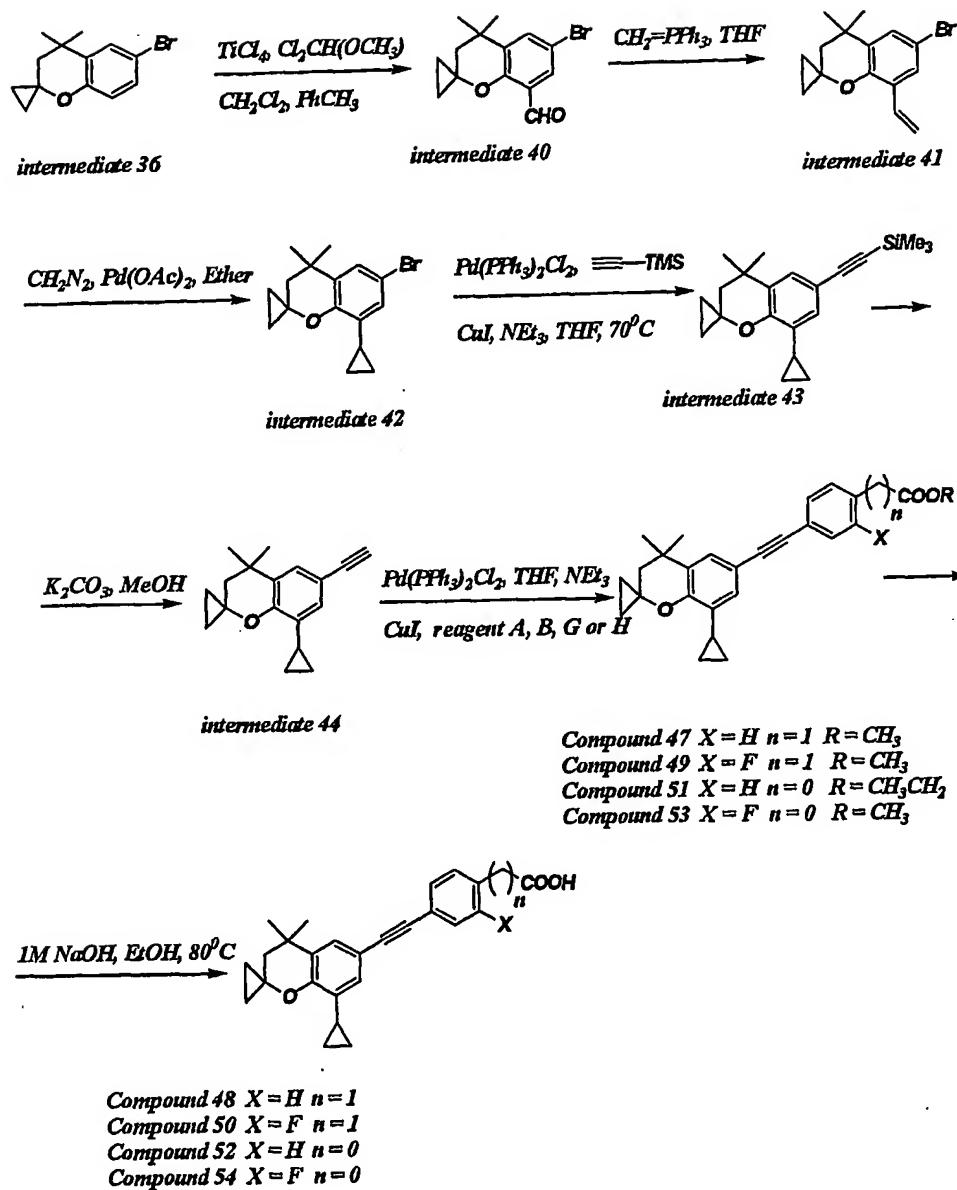
9 **Reaction Scheme 8** discloses presently preferred synthetic routes to
10 obtain other exemplary and preferred novel chroman compounds within the
11 scope of **Formula 1** where the symbol **X** represents oxygen (O), **Y** represents
12 a cyclopropyl group, **Z** is an ethynyl moiety and **A** is a substituted phenyl
13 moiety.



REACTION SCHEME 6



REACTION SCHEME 7



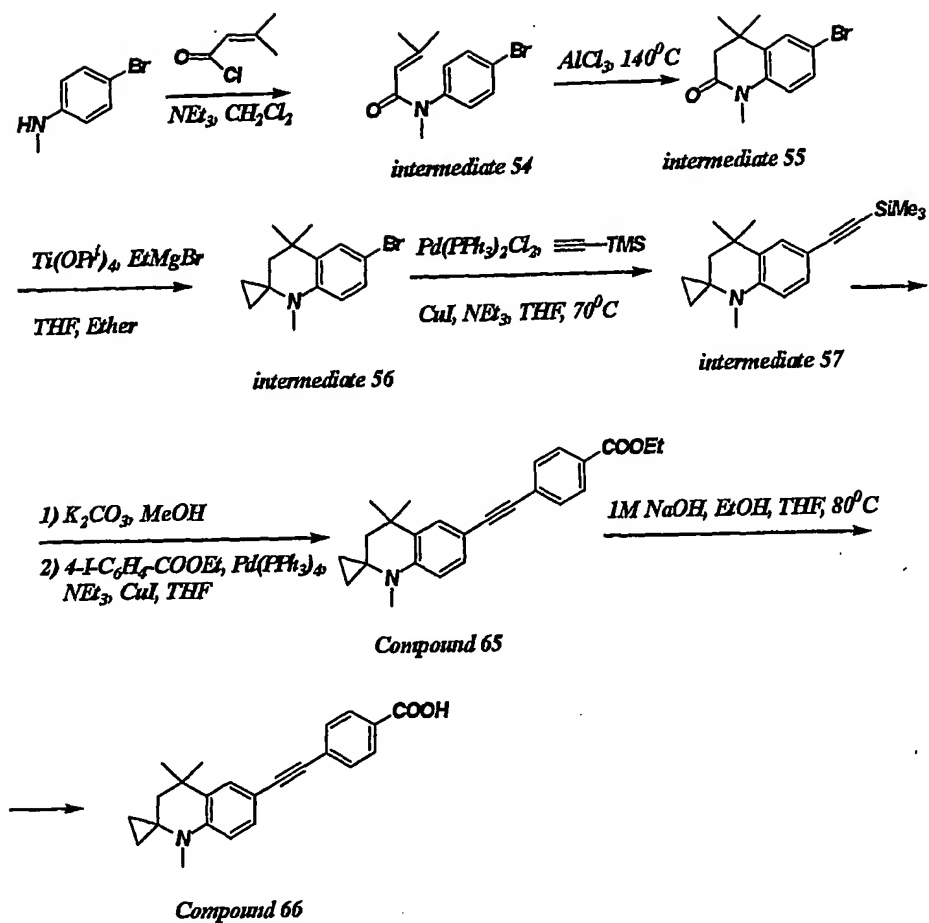
REACTION SCHEME 8

1 **Reaction Scheme 9** discloses presently preferred synthetic routes to
2 obtain exemplary and preferred novel tetrahydroquinoline compounds within
3 the scope of **Formula 1** where the symbol **X** represents an alkyl substituted
4 nitrogen (alkyl-N), **Y** represents hydrogen, **Z** is an ethynyl moiety and **A** is a
5 substituted phenyl moiety.

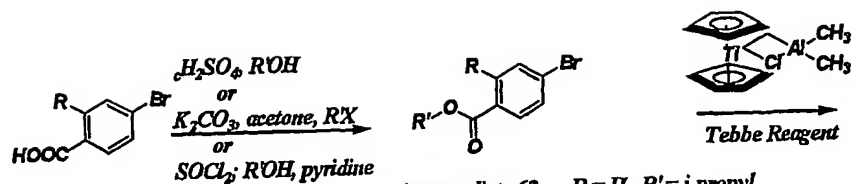
6 **Reaction Schemes 10 and 11** disclose presently preferred synthetic
7 routes to obtain exemplary and preferred novel phenyl compounds within the
8 scope of **Formula 2** where the symbol **X** represents oxygen (O), **R₅** is alkyl or
9 benzyl, **Z** is an ethynyl moiety and **A** is a substituted phenyl moiety.

10 **Reaction Scheme 12** discloses presently preferred synthetic routes to
11 obtain exemplary and preferred novel phenyl compounds within the scope of
12 **Formula 2** where the symbol **R₅-X** represents an alkyl, dialkyl, benzyl or
13 dibenzyl substituted nitrogen, **Z** is an ethynyl moiety and **A** is a substituted
14 phenyl moiety.

15 **Reaction Schemes 13 and 14** disclose presently preferred synthetic
16 routes to obtain exemplary and preferred novel phenyl compounds within the
17 scope of **Formula 6** where the symbol **X₂** represents a (1-imidazolyl) moiety,
18 **Z** is an ethynyl moiety and **A** is a substituted phenyl moiety.

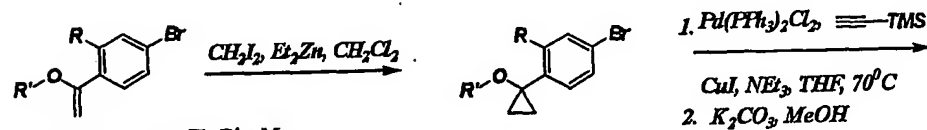


REACTION SCHEME 9



$R = H, Me, Et$

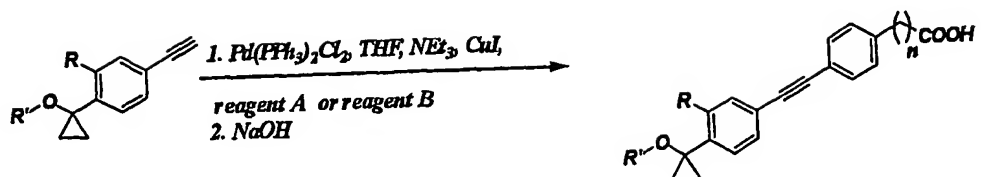
intermediate 62 $R = H$ $R' = i\text{-propyl}$
 intermediate 67 $R = H$ $R' = \text{benzyl}$
 intermediate 72 $R = Me$ $R' = \text{benzyl}$
 intermediate 77 $R = Me$ $R' = i\text{-propyl}$
 intermediate 82 $R = Me$ $R' = \text{neopentyl}$
 intermediate 86 $R = Et$ $R' = \text{benzyl}$
 intermediate 91 $R = Et$ $R' = i\text{-propyl}$



intermediate 58 $R = H$ $R' = Me$
 intermediate 63 $R = H$ $R' = i\text{-propyl}$
 intermediate 68 $R = H$ $R' = \text{benzyl}$
 intermediate 73 $R = Me$ $R' = \text{benzyl}$
 intermediate 78 $R = Me$ $R' = i\text{-propyl}$
 intermediate 83 $R = Me$ $R' = \text{neopentyl}$
 intermediate 87 $R = Et$ $R' = \text{benzyl}$
 intermediate 92 $R = Et$ $R' = i\text{-propyl}$

intermediate 59 $R = H$ $R' = Me$
 intermediate 64 $R = H$ $R' = i\text{-propyl}$
 intermediate 69 $R = H$ $R' = \text{benzyl}$
 intermediate 74 $R = Me$ $R' = \text{benzyl}$
 intermediate 79 $R = Me$ $R' = i\text{-propyl}$
 intermediate 84 $R = Me$ $R' = \text{neopentyl}$
 intermediate 88 $R = Et$ $R' = \text{benzyl}$
 intermediate 93 $R = Et$ $R' = i\text{-propyl}$

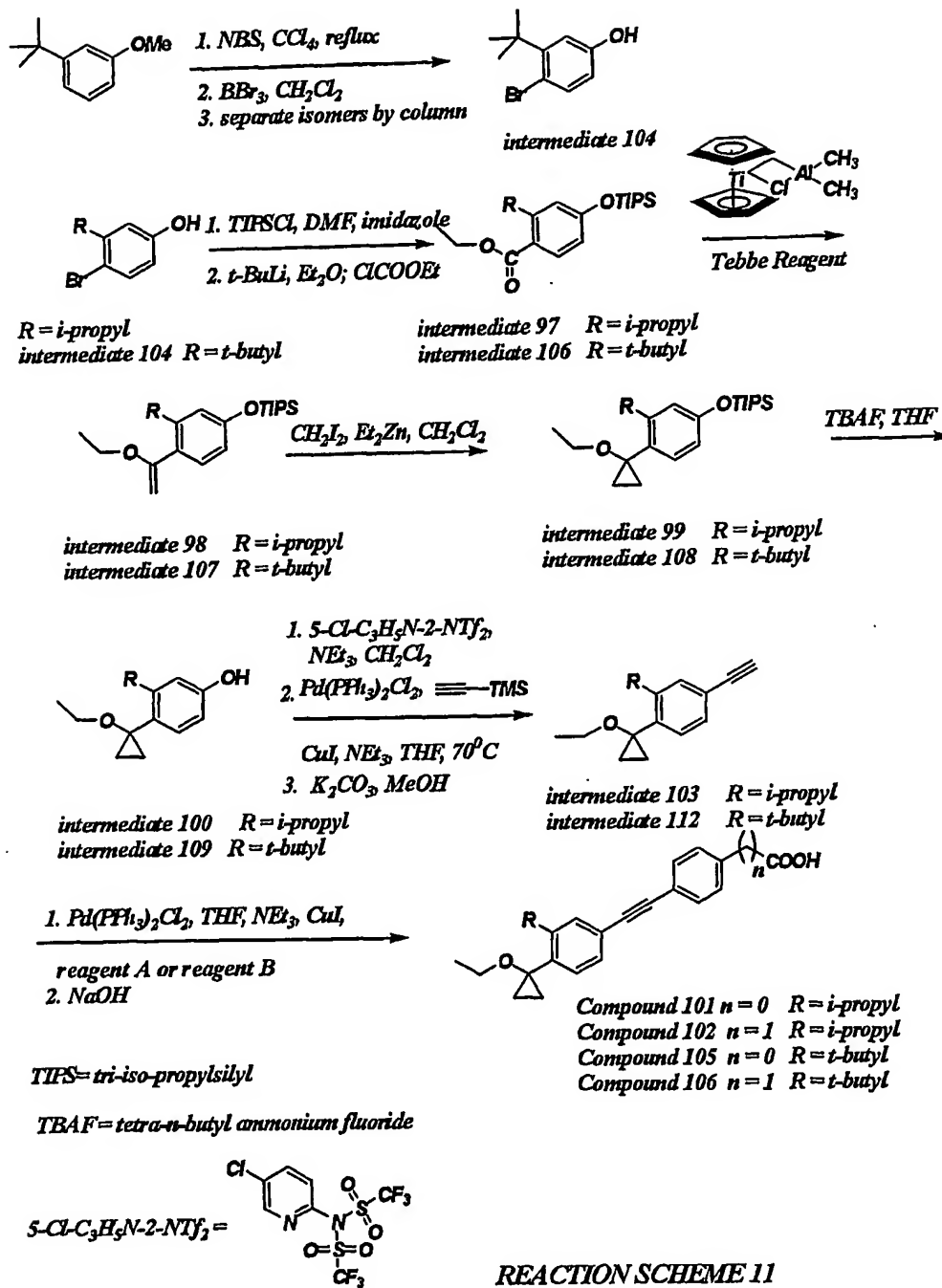
REACTION SCHEME 10

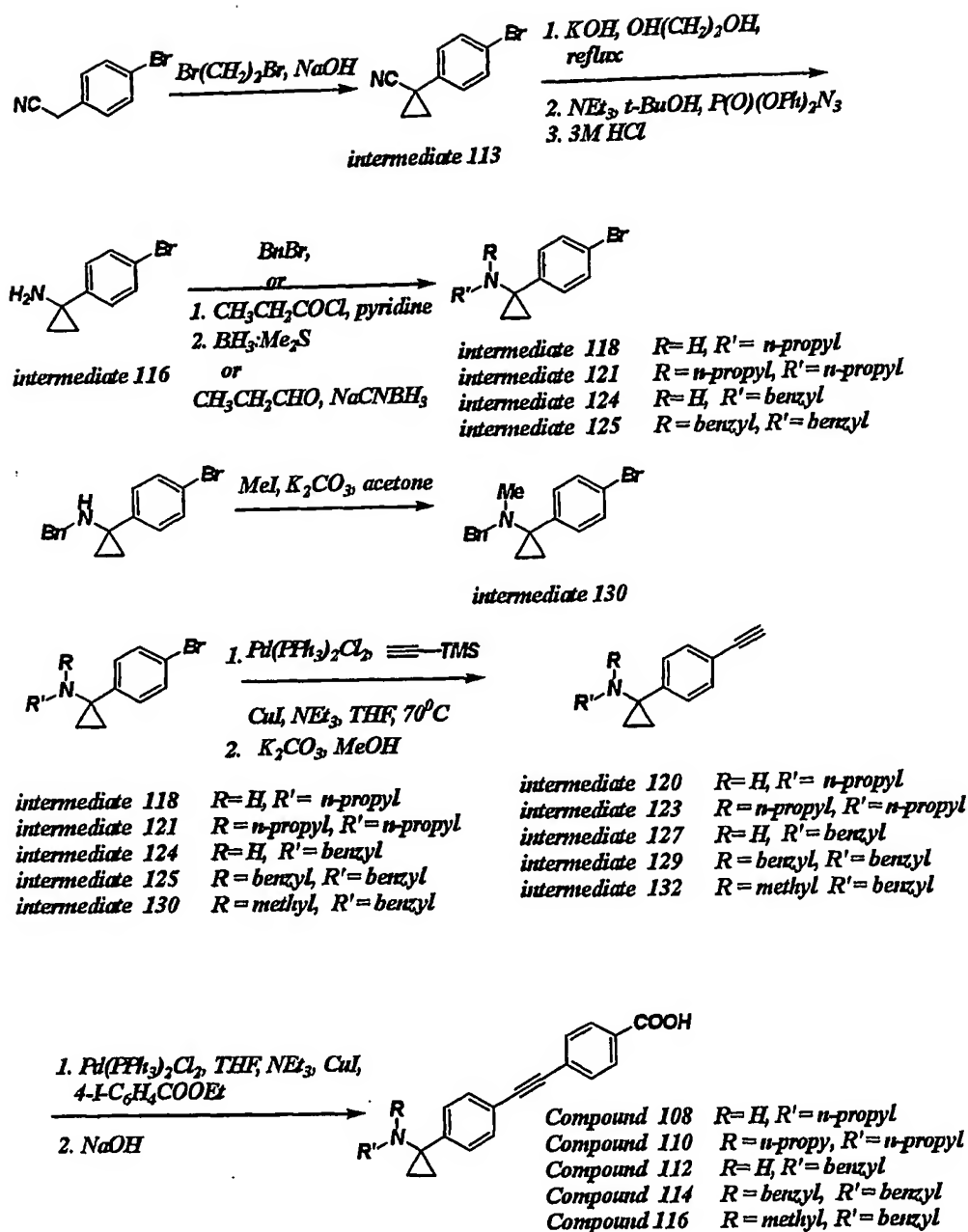


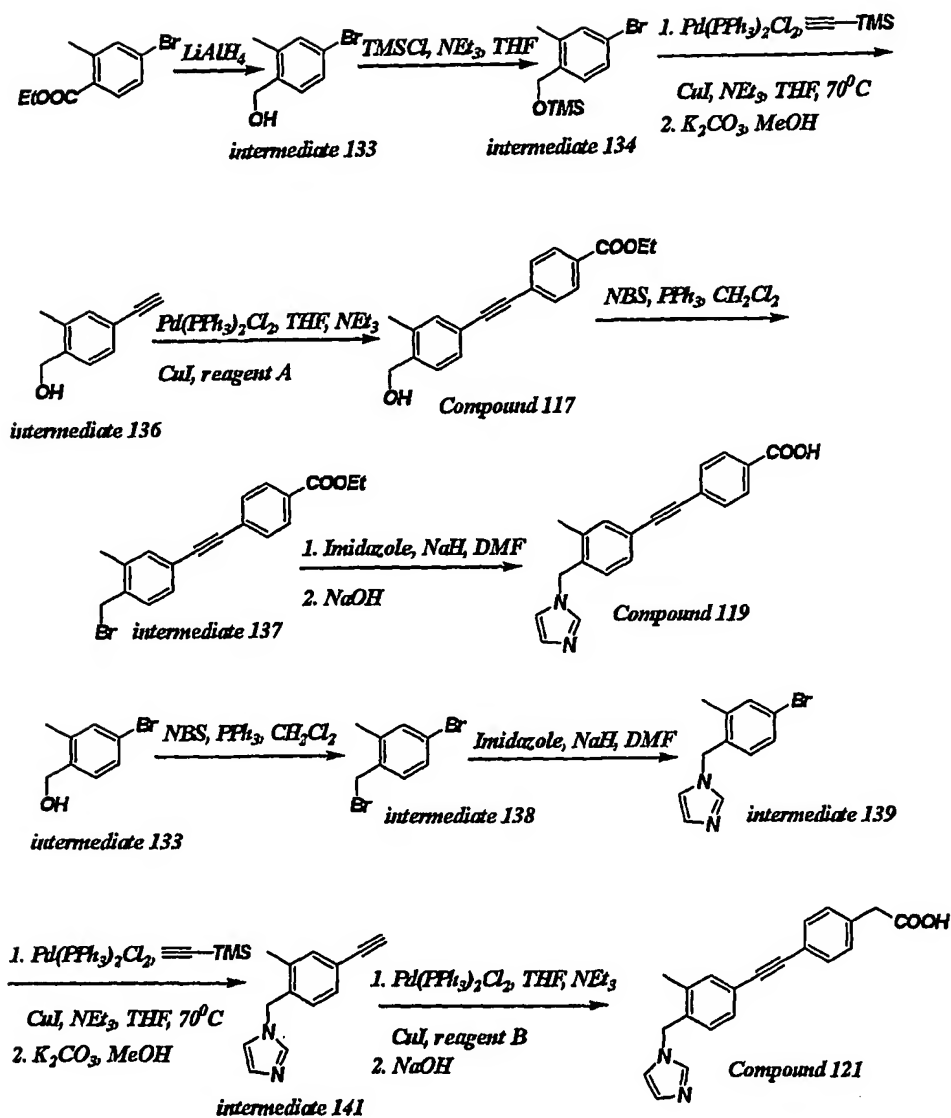
intermediate 61 $R = \text{H}$ $R' = \text{Me}$
 intermediate 66 $R = \text{H}$ $R' = \text{i-propyl}$
 intermediate 71 $R = \text{H}$ $R' = \text{benzyl}$
 intermediate 76 $R = \text{Me}$ $R' = \text{benzyl}$
 intermediate 81 $R = \text{Me}$ $R' = \text{i-propyl}$
 intermediate 85 $R = \text{Me}$ $R' = \text{neopentyl}$
 intermediate 90 $R = \text{Et}$ $R' = \text{benzyl}$
 intermediate 95 $R = \text{Et}$ $R' = \text{i-propyl}$

Compound 69 $n = 0$ $R = \text{H}$ $R' = \text{methyl}$
 Compound 70 $n = 1$ $R = \text{H}$ $R' = \text{methyl}$
 Compound 73 $n = 0$ $R = \text{H}$ $R' = \text{i-propyl}$
 Compound 74 $n = 1$ $R = \text{H}$ $R' = \text{i-propyl}$
 Compound 77 $n = 0$ $R = \text{H}$ $R' = \text{benzyl}$
 Compound 78 $n = 1$ $R = \text{H}$ $R' = \text{benzyl}$
 Compound 81 $n = 0$ $R = \text{Me}$ $R' = \text{benzyl}$
 Compound 82 $n = 1$ $R = \text{Me}$ $R' = \text{benzyl}$
 Compound 85 $n = 0$ $R = \text{Me}$ $R' = \text{i-propyl}$
 Compound 86 $n = 1$ $R = \text{Me}$ $R' = \text{i-propyl}$
 Compound 89 $n = 0$ $R = \text{Me}$ $R' = \text{neopentyl}$
 Compound 90 $n = 1$ $R = \text{Me}$ $R' = \text{neopentyl}$
 Compound 93 $n = 0$ $R = \text{Et}$ $R' = \text{benzyl}$
 Compound 94 $n = 1$ $R = \text{Et}$ $R' = \text{benzyl}$
 Compound 97 $n = 0$ $R = \text{Et}$ $R' = \text{i-propyl}$
 Compound 98 $n = 1$ $R = \text{Et}$ $R' = \text{i-propyl}$

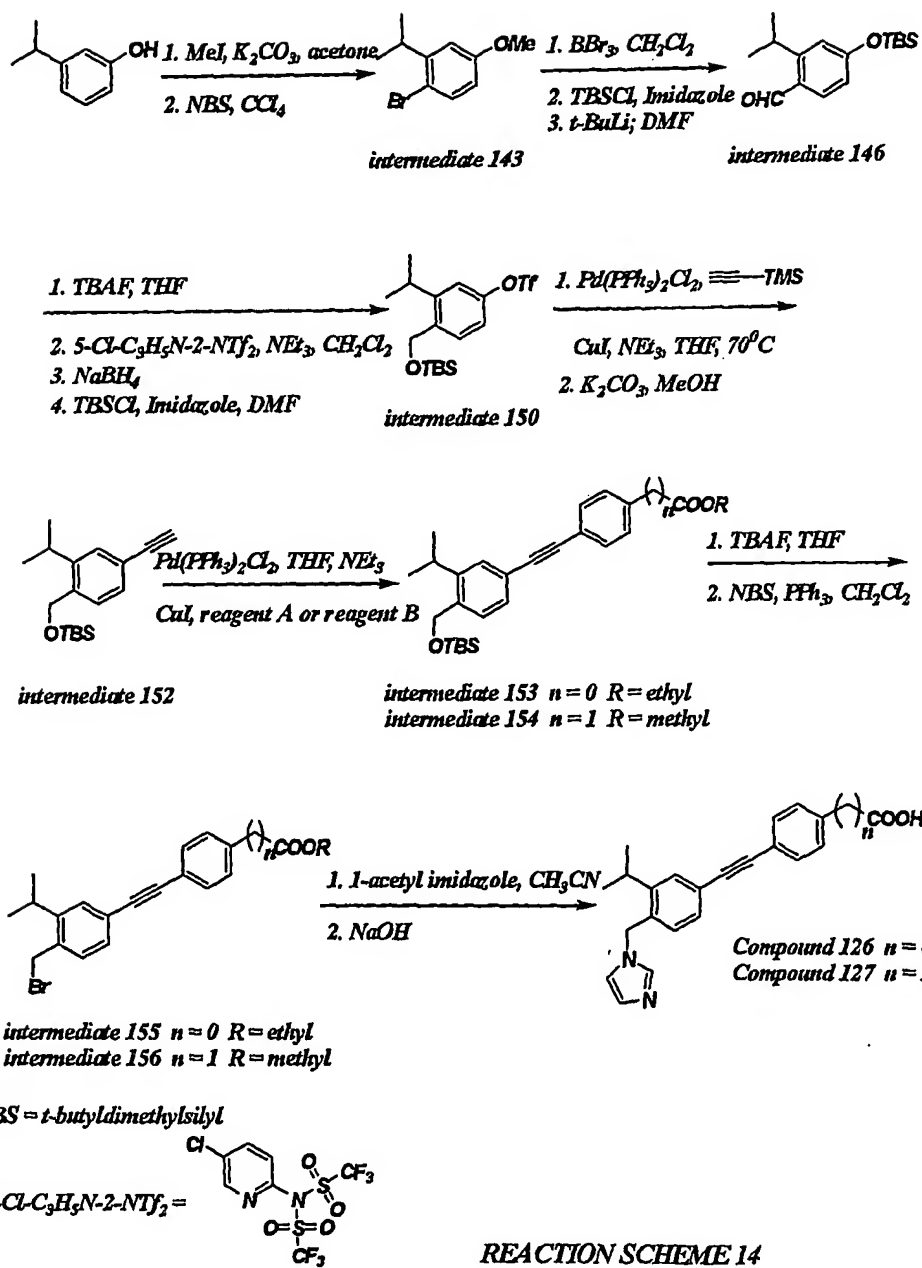
REACTION SCHEME 10 CONTINUED







REACTION SCHEME 13



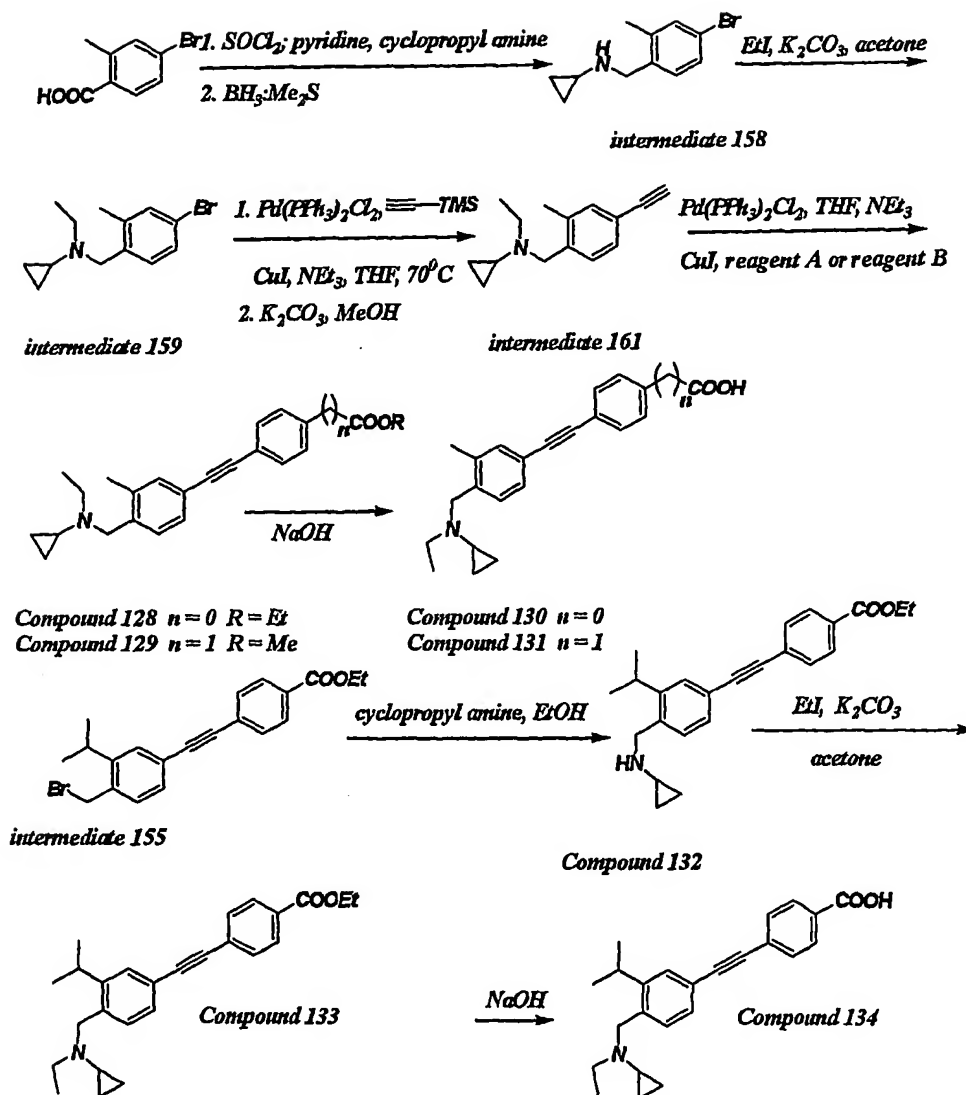
1 **Reaction Scheme 15** disclose presently preferred synthetic routes to
2 obtain exemplary and preferred novel phenyl compounds within the scope of
3 **Formula 6** where X_2 represents an alkyl and cyclopropyl substituted nitrogen
4 ($X_2 = (\text{alkyl, cycloalkyl})N$), Y represents hydrogen, Z is an ethynyl moiety
5 and A is a substituted phenyl moiety.

6 **Reaction Scheme 16** discloses presently preferred synthetic routes to
7 obtain exemplary and preferred novel tetrahydronaphthalene compounds
8 within the scope of **Formula 4** where the symbol X_1 represents a (1-
9 imidazolyl) moiety, Y represents hydrogen, Z is an ethynyl moiety and A is a
10 substituted phenyl moiety.

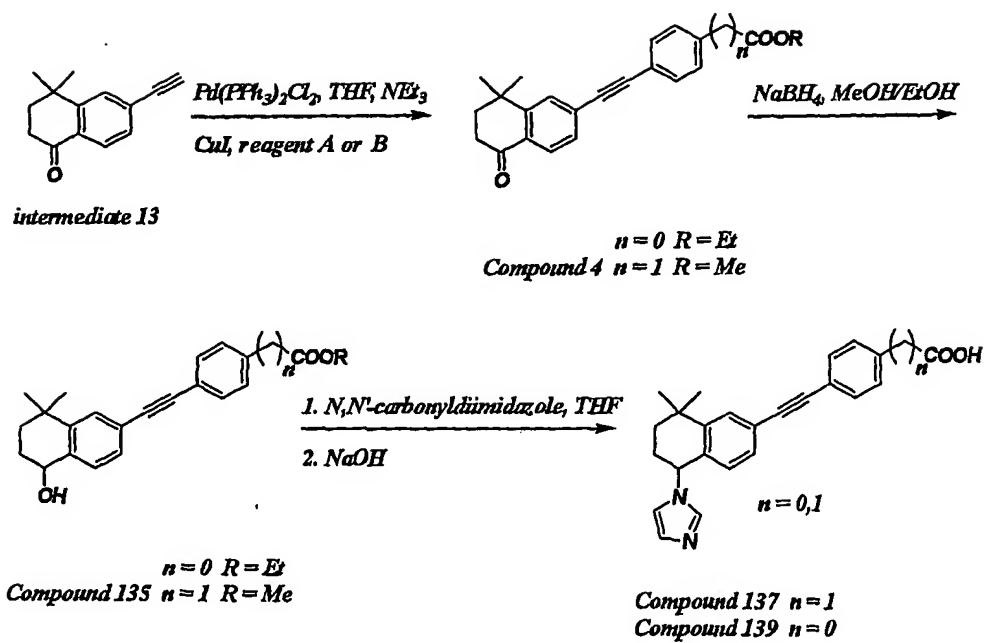
11 **Reaction Scheme 17** discloses presently preferred synthetic routes to
12 obtain exemplary and preferred novel phenyl compounds within the scope of
13 **Formula 6** where the symbol X_2 represents a 1-methyl-cyclopropoxy moiety,
14 Y represents hydrogen, Z is an ethynyl moiety and A is a substituted phenyl
15 moiety.

16 **Reaction Scheme 18** discloses presently preferred synthetic routes to
17 obtain exemplary and preferred novel phenyl compounds within the scope of
18 **Formula 5** where the symbol X represents oxygen (O), Y represents a
19 *tertiary*-butyl group, Z is an ethynyl moiety and A is a substituted phenyl
20 moiety.

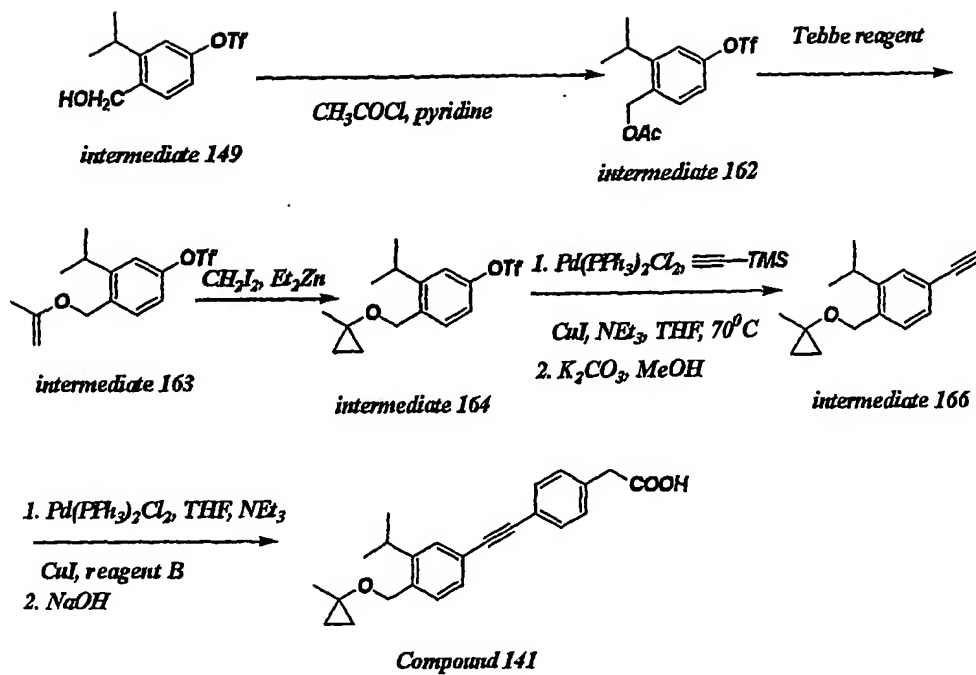
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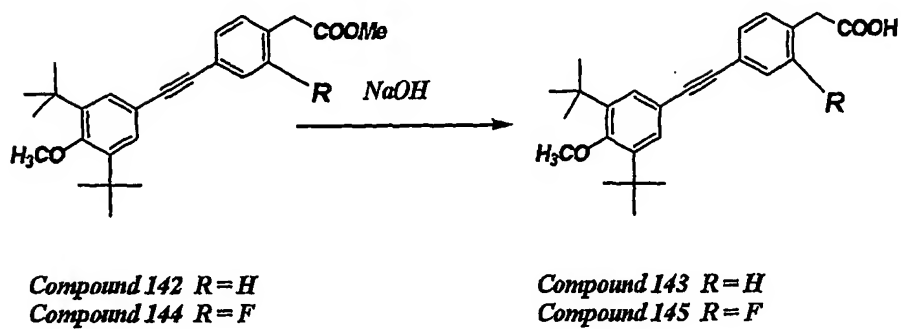
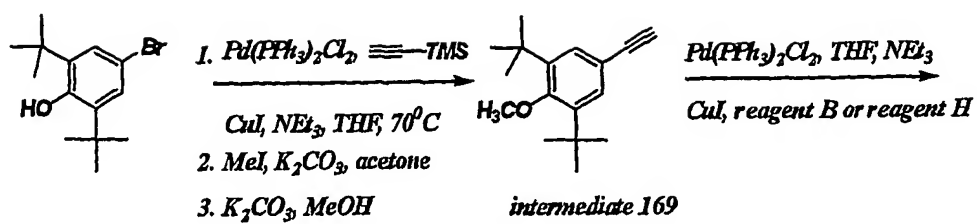
REACTION SCHEME 15



REACTION SCHEME 16

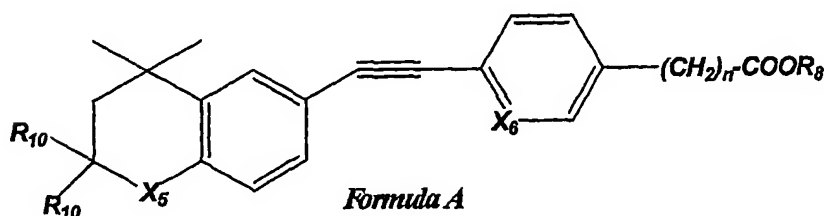


REACTION SCHEME 17



REACTION SCHEME 18

1 Certain known compounds which have been discovered in accordance
2 with the present invention to be useful as inhibitors of cytochrome P450RAI
3 are shown by **Formula A** where R_8 generally represents H, alkyl of 1 to 6
4 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
5 base, and where the other variables have the following specific values:



18 In **Compound 201** $X_5 = \text{O}$, $X_6 = \text{CH}$, $n = 0$, $R_8 = \text{H}$ or a cation of a
19 pharmaceutically acceptable base and $R_{10} = \text{CH}_3$.

20 In **Compound 202** $X_5 = \text{S}$, $X_6 = \text{CH}$, $n = 1$, $R_8 = \text{H}$ or a cation of a
21 pharmaceutically acceptable base and $R_{10} = \text{H}$.

22 In **Compound 210** $X_5 = \text{S}$, $X_6 = \text{CH}$, $n = 2$, $R_8 = \text{H}$ or a cation of a
23 pharmaceutically acceptable base and $R_{10} = \text{H}$.

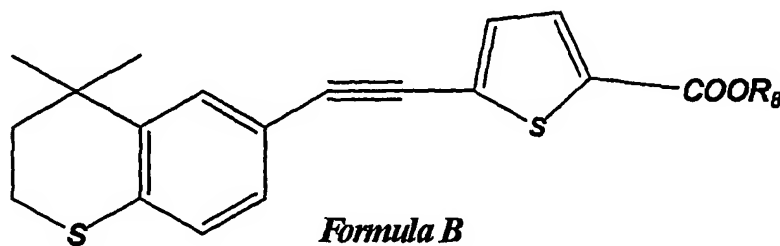
24 In **Compound 215** $X_5 = \text{S}$, $X_6 = \text{CH}$, $n = 0$, $R_8 = \text{H}$ or a cation of a
25 pharmaceutically acceptable base and $R_{10} = \text{H}$.

26 In **Compound 238** $X_5 = \text{S}$, $X_6 = \text{N}$, $n = 0$, $R_8 = \text{H}$ or a cation of a
27 pharmaceutically acceptable base, $R_{10} = \text{H}$.

28 **Compound 201** is described as compound 4 in United States Patent

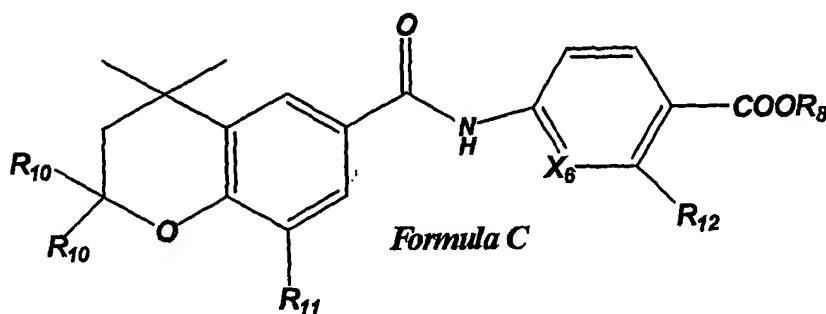
1 No. 4,980,369 incorporated herein by reference. **Compounds 202, 210, and**
2 **215** are described in United States Patent No. 4,810,804 incorporated herein
3 by reference. **Compound 215** is example 12 of Patent No. ,4810,804.
4 **Compound 238** is described in United States Patent No. 5,089,509
5 incorporated herein by reference (see Claim 5 of Patent No. 5,089,509).

6 Other known compounds which have been discovered in accordance
7 with the present invention to be useful as inhibitors of cytochrome P450RAI
8 are shown by **Formula B** where R_8 generally represents H, alkyl of 1 to 6
9 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
10 base.



21 Specifically in **Compound 240** R_8 is H or a cation of a pharmaceutically
22 acceptable base. **Compound 240** is described and can be made in accordance
23 with the teachings of United States Patent Nos. 5,089,509, ,5,602,130 or
24 5,348,972 all of which are incorporated herein by reference.

1 Still other known compounds which have been discovered in
2 accordance with the present invention to be useful as inhibitors of cytochrome
3 P450RAI are shown by **Formula C** where R_8 generally represents H, alkyl of
4 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
5 acceptable base, and where the other variables have the following specific
6 values:

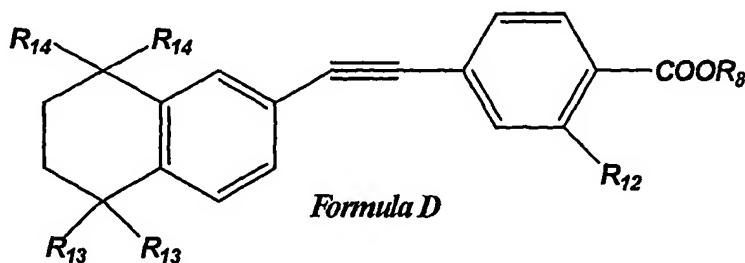


16 In **Compound 203** R_8 is H or a cation of a pharmaceutically acceptable base,
17 $R_{10} = \text{CH}_3$, $R_{11} = \text{Cl}$, $R_{12} = \text{F}$ and $X_6 = \text{CH}$.
18 In **Compound 204** R_8 is H or a cation of a pharmaceutically acceptable base,
19 $R_{10} = \text{CH}_3$, $R_{11} = \text{cyclopropyl}$, $R_{12} = \text{F}$ and $X_6 = \text{CH}$.
20 In **Compound 205** R_8 is H or a cation of a pharmaceutically acceptable base,
21 $R_{10} = \text{CH}_3$, $R_{11} = \text{CF}_3$, $R_{12} = \text{F}$ and $X_6 = \text{CH}$.
22 In **Compound 206** R_8 is H or a cation of a pharmaceutically acceptable base,
23 $R_{10} = \text{CH}_3\text{CH}_2$, $R_{11} = \text{Br}$, $R_{12} = \text{F}$ and $X_6 = \text{CH}$.
24 In **Compound 220** R_8 is H or a cation of a pharmaceutically acceptable base,
25 $R_{10} = \text{CH}_3$, $R_{11} = \text{CH}_3$, $R_{12} = \text{F}$ and $X_6 = \text{CH}$.
26 In **Compound 221** R_8 is H or a cation of a pharmaceutically acceptable base,
27 $R_{10} = \text{CH}_3$, $R_{11} = \text{Cl}$, $R_{12} = \text{F}$ and $X_6 = \text{N}$.
28 In **Compound 224** R_8 is H or a cation of a pharmaceutically acceptable base,

- 1 $R_{10} = CH_3$, $R_{11} = \text{phenyl}$, $R_{12} = F$ and $X_6 = CH$.
- 2 In Compound 225 R_8 is H or a cation of a pharmaceutically acceptable base,
- 3 $R_{10} = H$, $R_{11} = Br$, $R_{12} = F$ and $X_6 = CH$.
- 4 In Compound 226 R_8 is H or a cation of a pharmaceutically acceptable base,
- 5 $R_{10} = CH_3$, $R_{11} = OCH_3$, $R_{12} = F$ and $X_6 = CH$.
- 6 In Compound 227 R_8 is H or a cation of a pharmaceutically acceptable base,
- 7 $R_{10} = CH_3$, $R_{11} = CH_3$, $R_{12} = H$ and $X_6 = CH$.
- 8 In Compound 228 R_8 is H or a cation of a pharmaceutically acceptable base,
- 9 $R_{10} = CH_3$, $R_{11} = H$, $R_{12} = F$ and $X_6 = CH$.
- 10 In Compound 247 R_8 is H or a cation of a pharmaceutically acceptable base,
- 11 $R_{10} = CH_3$, $R_{11} = Br$, $R_{12} = F$ and $X_6 = CH$.
- 12 In Compound 248 R_8 is H or a cation of a pharmaceutically acceptable base,
- 13 $R_{10} = CH_3$, $R_{11} = CF_3CF_2$, $R_{12} = F$ and $X_6 = CH$.
- 14 In Compound 249 R_8 is H or a cation of a pharmaceutically acceptable base,
- 15 $R_{10} = CH_3$, $R_{11} = CH_3CH_2$, $R_{12} = F$ and $X_6 = CH$.
- 16 In Compound 250 R_8 is H or a cation of a pharmaceutically acceptable base,
- 17 $R_{10} = CH_3$, $R_{11} = \text{iso-propyl}$, $R_{12} = F$ and $X_6 = CH$.
- 18 In Compound 251 R_8 is H or a cation of a pharmaceutically acceptable base,
- 19 $R_{10} = CH_3$, $R_{11} = (1\text{-methyl})\text{cyclopropyl}$, $R_{12} = F$ and $X_6 = CH$.
- 20 In Compound 252 R_8 is H or a cation of a pharmaceutically acceptable base,
- 21 $R_{10} = CH_3$, $R_{11} = \text{tertiary-butyl}$, $R_{12} = F$ and $X_6 = CH$.
- 22 In Compound 253 R_8 is H or a cation of a pharmaceutically acceptable base,
- 23 $R_{10} = CH_3$, $R_{11} = (2,2\text{-difluoro})\text{cyclopropyl}$, $R_{12} = F$ and $X_6 = CH$.
- 24 In Compound 254 R_8 is H or a cation of a pharmaceutically acceptable base,
- 25 $R_{10} = CH_3$, $R_{11} = (\text{cyclopropyl})\text{methyl}$, $R_{12} = F$ and $X_6 = CH$.
- 26 Compounds 203 - 206, 220, 221, 224 - 228 and 247 - 254 are
- 27 described and can be made in accordance with the teachings of United States
- 28 Patent No: 5,675,024 which is incorporated herein by reference. (Compound

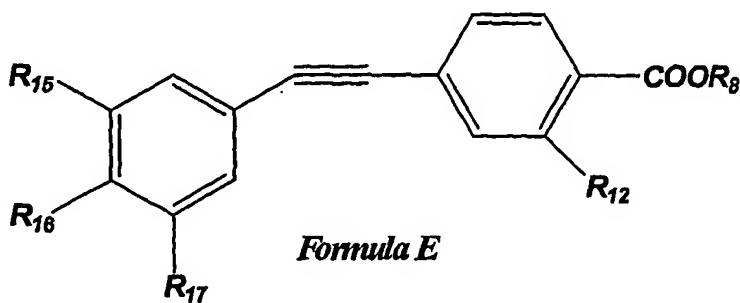
1 205 is compound or example 14, Compound 225 is compound or example 10,
2 and Compound 228 is compound or example 32 in Patent No. 5,675,024.
3 Compound 220 is also described in United States Patent No. 5,965,606,
4 incorporated herein by reference.

5 Still other known compounds which have been discovered in
6 accordance with the present invention to be useful as inhibitors of cytochrome
7 P450RAI are shown by Formula D where R_8 generally represents H, alkyl of
8 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
9 acceptable base, and where the other variables have the following specific
10 values:

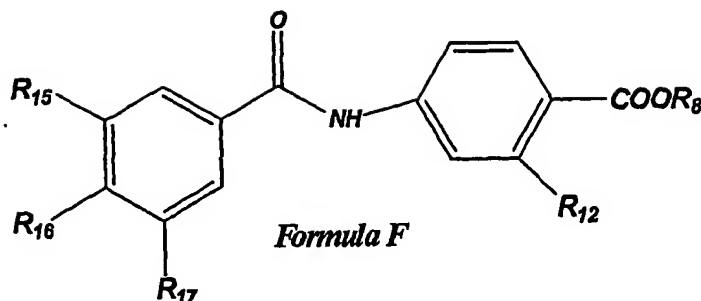


21 In Compound 207 R_8 is H or a cation of a pharmaceutically acceptable base,
22 R_{12} = H, the two R_{13} groups jointly represent an oxo (=O) function and R_{14} =
23 CH_3 .
24 In Compound 208 R_8 is H or a cation of a pharmaceutically acceptable base,
25 R_{12} = H, R_{13} = H and R_{14} = CH_3 .
26 In Compound 216 R_8 is H or a cation of a pharmaceutically acceptable base,
27 R_{12} = H, R_{13} = CH_3 and R_{14} = CH_3 .
28 In Compound 218 R_8 is H or a cation of a pharmaceutically acceptable base,

- 1 $R_{12} = H, R_{13} = CH_3$ and $R_{14} = H$.
2 In **Compound 230** R_8 is H or a cation of a pharmaceutically acceptable base,
3 $R_{12} = F, R_{13} = CH_3$ and $R_{14} = CH_3$.
4 In **Compound 232** R_8 is H or a cation of a pharmaceutically acceptable base,
5 $R_{12} = H$, one of the R_{13} groups is H, the other is OH and $R_{14} = CH_3$.
6 **Compound 207** is described (as compound 7) in United States Patent
7 No. 5,489,584 incorporated herein by reference. **Compound 232** is described
8 (as compound 42) in United States Patent No. 5,654,469 incorporated herein
9 by reference. **Compounds 208, 216 and 218** are described in the publication
10 by *Chandraratna et al.* J. Eur. J. Med. Chem., Suppl. to Vol. 30, 1995, 506s-
11 517s. **Compound 230** can also be made in accordance with the teachings of
12 the publication by *Chandraratna et al.* J. Eur. J. Med. Chem., Suppl to Vol.
13 30, 1995, 506s-517s, incorporated herein by reference, or by such modification
14 of the synthetic procedures of this reference which will be readily apparent to
15 those skilled in the art.
16 Still further known compounds which have been discovered in
17 accordance with the present invention to be useful as inhibitors of cytochrome
18 P450RAI are shown by **Formula E** where R_8 generally represents H, alkyl of
19 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
20 acceptable base, and where the other variables have the following specific
21 values:



- 1 In **Compound 209** R_8 is H or a cation of a pharmaceutically acceptable base,
2 $R_{12} = H$, $R_{15} = \text{tertiary-butyl}$, $R_{16} = OH$ and $R_{17} = Cl$.
3 In **Compound 211** R_8 is H or a cation of a pharmaceutically acceptable base,
4 $R_{12} = H$, $R_{15} = \text{tertiary-butyl}$, $R_{16} = OCH_3$ and $R_{17} = \text{tertiary-butyl}$.
5 In **Compound 214** R_8 is H or a cation of a pharmaceutically acceptable base,
6 $R_{12} = H$, $R_{15} = 1\text{-adamantyl}$, $R_{16} = OCH_3$ and $R_{17} = H$.
7 In **Compound 235** R_8 is H or a cation of a pharmaceutically acceptable base,
8 $R_{12} = H$, $R_{15} = \text{tertiary-butyl}$, $R_{16} = OH$ and $R_{17} = \text{tertiary-butyl}$.
9 In **Compound 236** R_8 is H or a cation of a pharmaceutically acceptable base,
10 $R_{12} = F$, $R_{15} = \text{tertiary-butyl}$, $R_{16} = OH$ and $R_{17} = H$.
11 **Compound 211** is described and can be made in accordance with the
12 teachings of United States Patent No. 5,202,471, and **Compound 235** is
13 described and can be made in accordance with the teachings of United States
14 Patent No. 5,498,795. The specification of Patent Nos. 5,202,471 and
15 5,498,795 are incorporated herein by reference. **Compounds 209, 214** and
16 **236** can also be made in accordance with the teachings of United States Patent
17 Nos. 5,202,471 and 5,498,795 with such modifications of the synthetic
18 procedures which will be readily apparent to those skilled in the art.
19 Still more known compounds which have been discovered in
20 accordance with the present invention to be useful as inhibitors of cytochrome
21 P450RAI are shown by **Formula F** where R_8 generally represents H, alkyl of
22 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
23 acceptable base, and where the other variables have the following specific
24 values:

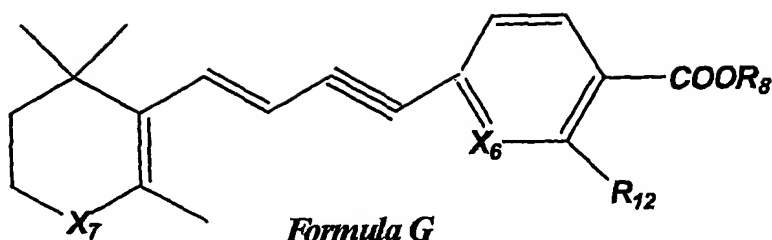


11 In Compound 222 R_8 is H or a cation of a pharmaceutically acceptable base,
12 $R_{12} = F$, $R_{15} = \text{tertiary-butyl}$, $R_{16} = \text{CH}_3\text{CH}_2\text{O}$ and $R_{17} = \text{I}$.

13 In Compound 223 R_8 is H or a cation of a pharmaceutically acceptable base,
14 $R_{12} = F$, $R_{15} = \text{tertiary-butyl}$, $R_{16} = \text{CH}_3\text{CH}_2\text{O}$ and $R_{17} = \text{Br}$.

15 Compounds 222 and 223 are described and can be made in accordance
16 with the teachings of United States Patent Nos. 5,663,357 and 5,917,048, the
17 specifications of which are incorporated herein by reference.

18 Yet more known compounds which have been discovered in
19 accordance with the present invention to be useful as inhibitors of cytochrome
20 P450RA1 are shown by Formula G where R_8 generally represents H, alkyl of
21 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
22 acceptable base, and where the other variables have the following specific
23 values:



11 In **Compound 212** R_8 is H or a cation of a pharmaceutically acceptable base,

12 $R_{12} = H$, $X_6 = CH$ and $X_7 = (CH_3)_2C$.

13 In **Compound 217** R_8 is H or a cation of a pharmaceutically acceptable base,

14 $R_{12} = H$, $X_6 = CH$ and $X_7 = CH_2$.

15 In **Compound 219** R_8 is H or a cation of a pharmaceutically acceptable base,

16 $R_{12} = H$, $X_6 = CH$ and $X_7 = S$.

17 In **Compound 229** R_8 is H or a cation of a pharmaceutically acceptable base,

18 $R_{12} = F$, $X_6 = CH$ and $X_7 = CH_2$.

19 In **Compound 244** R_8 is H or a cation of a pharmaceutically acceptable base,

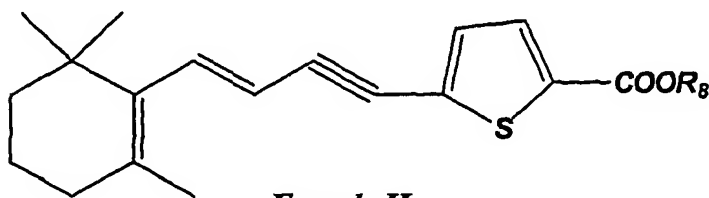
20 $R_{12} = H$, $X_6 = N$ and $X_7 = CH_2$.

21 **Compounds 217** is described (as example or compound 4) and can be
22 made in accordance with the teachings of United States Patent Nos. 4,739,098
23 the specification of which is incorporated herein by reference. **Compounds**

24 **219** is described (as compound 2) and can be made in accordance with the
25 teachings of United States Patent Nos. 5,688,957, the specification of which is
26 incorporated herein by reference. **Compound 212** and **Compound 229** can be
27 made in accordance with the teachings of United States Patent Nos. 4,739,098
28 and in case of **Compound 212** also in accordance with United States Patent

1 No. 5,426,118, with such modifications of the synthetic procedures which will
2 be readily apparent to those skilled in the art. The specification of United
3 States Patent No. 5,426,118 is incorporated herein by reference. **Compound**
4 **244** is described (as compound or example 7) and can be made in accordance
5 with the teachings of United States Patent Nos. 4,923,884, the specification of
6 which is incorporated herein by reference.

7 Still more known compounds which have been discovered in
8 accordance with the present invention to be useful as inhibitors of cytochrome
9 P450RAI are shown by **Formula H** where R_8 generally represents H, alkyl of
10 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
11 acceptable base.



Formula H

23 Specifically in **Compound 245** R_8 is H or a cation of a pharmaceutically
24 acceptable base.

25 **Compounds 245** is described and can be made in accordance with the
26 teachings of United States Patent Nos. 4,923,884.

1 Further known compounds which have been discovered in accordance
2 with the present invention to be useful as inhibitors of cytochrome P450RAI
3 are shown by **Formula I** where R_8 generally represents H, alkyl of 1 to 6
4 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
5 base.

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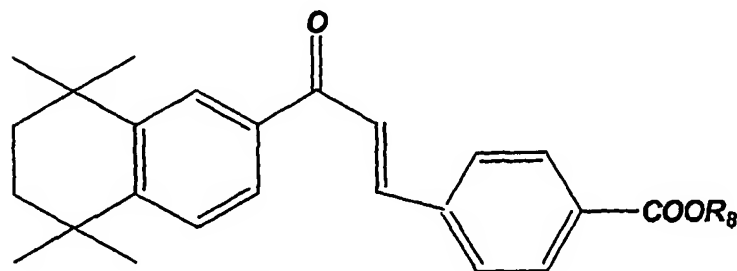
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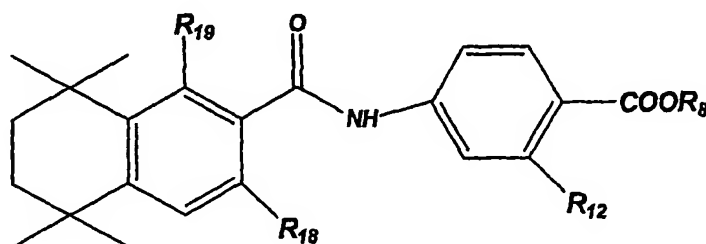


Formula I

17 Specifically in **Compound 242** R_8 is H or a cation of a pharmaceutically
18 acceptable base.

19 **Compound 242** is described in the publication by *Bernard et al.*
20 *Biochem. Biophys. Res. Commun.*, 1992, Vol. 186, 977-983, incorporated
21 herein by reference.

1 Still more known compounds which have been discovered in
2 accordance with the present invention to be useful as inhibitors of cytochrome
3 P450RAI are shown by **Formula J** where R_8 generally represents H, alkyl of
4 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
5 acceptable base, and where the other variables have the following specific
6 values:

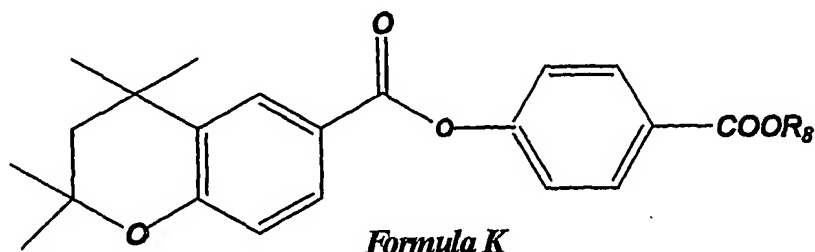


Formula J

18 In **Compound 237** R_8 is H or a cation of a pharmaceutically acceptable base,
19 $R_{12} = \text{F}$, $R_{18} = \text{H}$ and $R_{19} = \text{H}$.
20 In **Compound 246** R_8 is H or a cation of a pharmaceutically acceptable base,
21 $R_{12} = \text{H}$, $R_{18} = \text{OH}$ and $R_{19} = \text{F}$.

22 **Compounds 237 and 246** are described and can be made in accordance
23 with the teachings of United States Patent Nos. 5,675,024 and 5,856,490.
24 **Compound 237** is compound or example 2 of Patent No. 5,675,024. The
25 specification of United States Patent No. 5,856,490 is incorporated herein by
26 reference.

1 Additional known compounds which have been discovered in
2 accordance with the present invention to be useful as inhibitors of cytochrome
3 P450RAI are shown by **Formula K** where R_8 generally represents H, alkyl of
4 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
5 acceptable base.



17 Specifically in **Compound 231** R_8 is H or a cation of a pharmaceutically
18 acceptable base.

19 **Compound 231** is described (as compound 2) in United States Patent
20 No. 5,006,550, the specification of which is incorporated herein by reference.

1 Still more known compounds which have been discovered in
2 accordance with the present invention to be useful as inhibitors of cytochrome
3 P450RAI are shown by **Formula L** where R_8 generally represents H, alkyl of
4 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
5 acceptable base.

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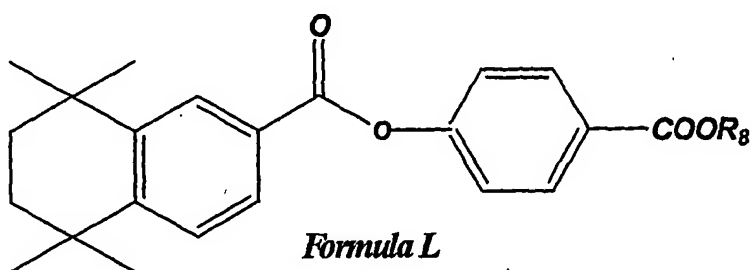
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16 Specifically in **Compound 243** R_8 is H or a cation of a pharmaceutically
17 acceptable base.

18 **Compound 243** is described (as example or compound 7) in United
19 States Patent No. 5,130,335, the specification of which is incorporated herein
20 by reference.

21



1 Still more known compounds which have been discovered in
2 accordance with the present invention to be useful as inhibitors of cytochrome
3 P450RAI are shown by **Formula M** where R_8 generally represents H, alkyl of
4 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
5 acceptable base, and where the other variables have the following specific
6 values:

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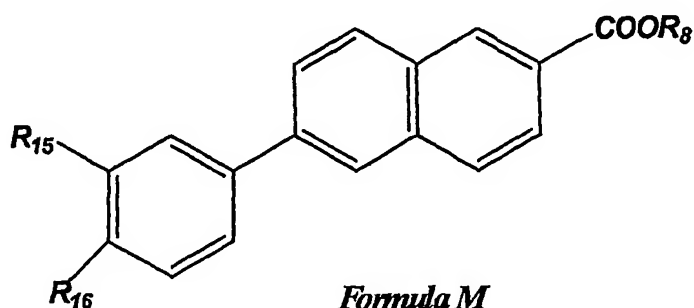
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Formula M

16 In **Compound 233** R_8 is H or a cation of a pharmaceutically acceptable base,
17 $R_{15} = 1\text{-adamantyl}$ and $R_{16} = \text{OH}$.

18 In **Compound 234** R_8 is H or a cation of a pharmaceutically acceptable base,
19 $R_{15} = 1\text{-adamantyl}$ and $R_{16} = \text{OCH}_3$.

20 **Compounds 233 and 234** are described in the publication by *Shroot et*
21 *al.* J. M. EP 199636 (1986) incorporated herein by reference.

1 Further known compounds which have been discovered in accordance
2 with the present invention to be useful as inhibitors of cytochrome P450RAI
3 are shown by **Formula N** where R_8 generally represents H, alkyl of 1 to 6
4 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
5 base.

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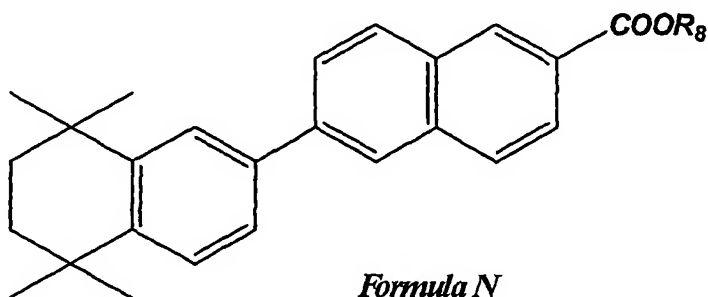
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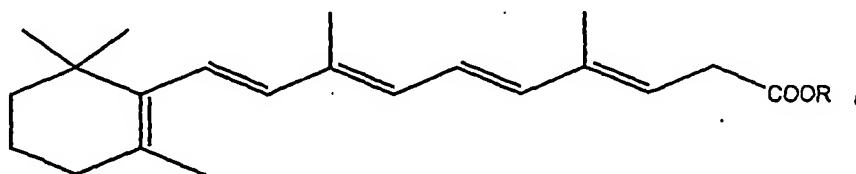
17 Specifically in **Compound 241** R_8 is H or a cation of a pharmaceutically
18 acceptable base.

19 **Compound 241** is described in the publication by *Dawson et al.* J.
20 Med. Chem., 1983, Vol. 26, 1653-1656. incorporated herein by reference.



Formula N

1 Still further compounds which have been discovered in accordance with
2 the present invention to be useful as inhibitors of cytochrome P450RAI are
3 shown by **Formula O** where R_8 generally represents H, alkyl of 1 to 6
4 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base.



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12 **Formula O**

13 Specifically in **Compound 247** R_8 is H or a cation of a
14 pharmaceutically acceptable base. Compound 247 is described in the
15 publication by *Winum et al.* Il Farmaco, 1997, Vol. 52, 1, p39-42, incorporated
16 herein by reference.

17 The P450RAI inhibition data of this compound are provided in **Table**
18 **1A**, and the cutaneous toxicity score (blackjack score) of the compound in the
19 topical skin irritation tests provided above, are disclosed in **Table 1B**.

1 SPECIFIC EXAMPLES OF NEW COMPOUNDS

2 4-Hydroxy phenyl acetic acid-*t*-butyl ester (Reagent E)

3 A stirred suspension of 4-hydroxy-phenyl acetic acid (0.152g, 1mmol)
4 in anhydrous toluene (5mL) was heated at 80°C and N,N-dimethyl formamide-
5 di-*t*-butyl acetal (1mL, 4.17mmol) was added when the solution became
6 homogenous. After 0.5h, the reaction mixture was cooled to ambient
7 temperature and the volatiles were distilled off in *vacuo*. The residue was
8 diluted with water and extracted with diethyl ether (x2). The combined
9 organic extract was dried over anhydrous sodium sulfate, filtered and
10 evaporated in *vacuo* to afford an oil which was subjected to flash column
11 chromatography over silica gel (230-400 mesh) using 16% ethyl acetate in
12 hexane as the eluent to afford the title compound as a solid (0.11g, 56%).
13 ¹H-NMR (300 MHz, CDCl₃): δ 1.44(s, 9H), 3.45(s, 2H), 6.55(s, 1H), 6.69(d, *J*
14 = 8.8Hz, 2H), 7.06(d, *J* = 8.5Hz, 2H).

15 3-Hydroxy phenyl acetic acid-*t*-butyl ester (Reagent F)

16 A stirred suspension of 3-hydroxy-phenyl acetic acid (1.52g, 10mmol)
17 in anhydrous toluene (20mL) was heated at 80°C and N,N-dimethyl
18 formamide-di-*t*-butyl acetal (9.6mL, 40mmol) was added when the solution
19 became homogenous. After 0.5h, the reaction mixture was cooled to ambient
20 temperature and the volatiles were distilled off in *vacuo*. Th residue was
21 diluted with water and extracted with diethyl ether (x2). The combined
22 organic extract was dried over anhydrous sodium sulfate, filtered and
23 evaporated in *vacuo* to afford an oil which was subjected to flash column
24 chromatography over silica gel (230-400 mesh) using 16% ethyl acetate in
25 hexane as the eluent to afford the title compound as a solid (1.17g, 56%).
26 ¹H-NMR (300 MHz, CDCl₃): δ 1.47(s, 9H), 3.49(s, 2H), 6.30(s, 1H), 6.70-6.79
27 (m, 2H), 6.81(d, *J* = 7.6Hz, 1H), 7.16(t, *J* = 7.7Hz, 1H).

28 Methyl-2-fluoro-4-iodo benzoate (Reagent G)

1 A solution of 2-fluoro-4-iodo toluene (5g, 26.6mmol) in pyridine (2mL)
2 and water (20mL) was treated with potassium permanganate (16.6g,
3 105mmol) and heated at 150°C overnight. The reaction mixture was then
4 cooled to room temperature and filtered and the filtrate was extracted with
5 hexane. The aqueous phase was acidified with 10% hydrochloric acid and
6 extracted with ethyl acetate. The organic phase was dried over anhydrous
7 sodium sulfate, filtered and evaporated in *vacuo*. The residue was dissolved
8 in 20mL of methanol, treated with concentrated sulfuric acid (1mL) and
9 refluxed overnight. The volatiles were distilled off in *vacuo* and the residue
10 was dissolved in diethyl ether, washed with brine, dried over anhydrous
11 sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash column
12 chromatography over silica gel (230-400 mesh) using 10% ethyl acetate in
13 hexane as the eluent afforded the title compound as an oil (0.26g, 5%).

14 ¹H NMR (300 MHz, CDCl₃): δ 7.60 (m, 4H), 3.93 (s, 3H).

15 Ethyl-2-fluoro-4-hydroxy benzoate (Reagent I)

16 A solution of 2-fluoro-4-hydroxy benzoic acid (**Intermediate 4**, 3g,
17 19.2mmol) in ethanol (65mL) and benzene (90mL) was treated with
18 concentrated sulfuric acid (1.5mL) and heated at reflux overnight using a
19 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the
20 residue was diluted with water and diethyl ether. The phases were separated
21 and the organic phase was washed with saturated aqueous sodium bicarbonate
22 (x1), water (x1) and brine (x1), dried over anhydrous magnesium sulfate,
23 filtered and evaporated in *vacuo* to afford the title compound as a solid (3.07g,
24 86%).

25 ¹H-NMR (300 MHz, CD₃COCD₃): δ 1.34 (t, *J* = 7.1Hz, 3H), 4.32 (q, *J* =
26 7.1Hz, 2H), 6.66(dd, *J* = 2.6, 10.9Hz, 1H), 6.76 (dd, *J* = 2.3, 8.5Hz, 1H),
27 7.83(d, *J* = 8.4Hz, 1H), 9.91 (s, 1H).

28 Ethyl-2-fluoro-4-trifluoromethylsulfonyloxy-benzoate (Intermediate 6)

29 A stirred, cooled (ice bath) solution of ethyl-2-fluoro-4-hydroxy-

1 benzoate (**Intermediate 5**, 0.368g, 2mmol) and 2,6-di-*tert*-butyl-4-methyl-
2 pyridine (0.81g, 8mmol) in 8mL of dichloromethane was treated with
3 trifluoromethanesulfonic anhydride (0.1g, 4mmol). The reaction mixture was
4 allowed to warm to ambient temperature and stirred overnight. The reaction
5 mixture was subjected to flash column chromatography over silica gel (230-
6 400 mesh) using 5-10% ethyl acetate in hexane as the eluent to afford the title
7 compound (0.53g, 85%).

8 ¹H-NMR (300 MHz, CDCl₃): δ 1.41 (t, *J* = 7.3Hz, 3H), 4.42 (q, *J* = 7.1Hz,
9 2H), 7.12-7.20(m, 2H), 8.08(t, *J* = 8.3Hz, 1H).

10 Ethyl-2-fluoro-4-trimethylsilanylethynyl-benzoate (**Intermediate 7**)

11 A solution of ethyl-2-fluoro-4- trifluoromethylsulfonyloxy-benzoate
12 (**Intermediate 6**, 1.82g, 6mmol) in triethyl amine (12mL) and anhydrous
13 tetrahydrofuran (30mL) was treated with copper(I)iodide (0.12g, 0.6mmol)
14 and sparged with argon. Dichlorobis(triphenylphosphine)palladium(II) (0.43g,
15 0.6mmol) was added followed by (trimethylsilyl)acetylene (3.6mL, 24mmol)
16 and the resulting reaction mixture was heated at 70°C overnight. It was then
17 cooled to ambient temperature, diluted with diethyl ether and filtered over a
18 bed of celite. The filtrate was evaporated in *vacuo* to an oil which was
19 subjected to flash column chromatography over silica gel (230-400 mesh)
20 using 5% ethyl acetate in hexane as the eluent to afford the title compound as
21 an orange oil (1.5g, quantitative).

22 ¹H-NMR (300 MHz, CDCl₃):δ 0.011 (s, 9H), 1.13(t, *J* = 7.1Hz, 3H), 4.13 (q, *J*
23 = 7.1Hz, 2H), 6.93-7.02(m, 2H), 7.07 (s, 1H), 7.61(t, *J* = 7.9Hz, 1H).

24 Ethyl-4-ethynyl-2-fluoro benzoate (**Reagent D**)

25 A solution of ethyl-2-fluoro-4-trimethylsilanylethynyl-benzoate
26 (**Intermediate 7**, 1.5g, 6mmol) in ethanol (16mL) was treated with potassium
27 carbonate (1.485g, 10.74mmol) and stirred overnight at room temperature.
28 The reaction mixture was then diluted with water and extracted with diethyl
29 ether (x2). The combined organic phase was dried over anhydrous magnesium

1 sulfate, filtered and evaporated in *vacuo* to afford an orange oil. Flash column
2 chromatography over silica gel (230-400 mesh) using 5% ethyl acetate in
3 hexane as the eluent afforded the title compound (1g, 86%).
4 ¹H-NMR (300 MHz, CDCl₃): δ 1.39 (t, *J* = 7.1Hz, 3H), 3.26 (s, 1H), 4.39 (q, *J*
5 = 7.1Hz, 2H), 7.22-7.33 (m, 2H), 7.88(t, *J* = 7.7Hz, 1H).

6 Methyl-4-iodo-phenyl acetate (Reagent B)

7 A solution of 4-iodo phenyl acetic acid (5g, 19mmol) in methanol was
8 treated with concentrated sulfuric acid (0.5mL) and refluxed overnight. The
9 volatiles were distilled off in *vacuo* and the residue was dissolved in ethyl
10 acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and
11 evaporated in *vacuo* to an oil which was subjected to flash column
12 chromatography over silica gel (230-400 mesh) using 5% ethyl acetate in
13 hexane as the eluent to afford the title compound as a clear oil (5g, 95%).
14 ¹H NMR (300 MHz, CDCl₃): δ 7.63 (d, 2H, *J* = 8.5Hz), 7.01 (d, 2H, *J* =
15 8.0Hz), 3.67 (s, 3H), 3.55 (s, 2H).

16 2-Fluoro-4-iodo-phenyl acetonitrile (Intermediate 2)

17 A solution of 2-fluoro-4-iodo-benzyl bromide (**Intermediate 1**, 2.56g,
18 8.15mmol) in ethanol (55mL and water (10mL) was treated with sodium
19 cyanide (2.15g, 43.86mmol) and refluxed for 0.5h. The volatiles were distilled
20 off in *vacuo* and the residue was diluted with water and extracted with diethyl
21 ether (x2). The combined organic extract was washed with water (x1) and
22 brine (x1), dried over anhydrous magnesium sulfate, filtered and evaporated in
23 *vacuo* to afford the title compound as a pale yellow solid (2.05g, 96%).
24 ¹H-NMR (300 MHz, CDCl₃): δ 3.71(s, 3H), 7.16(t, *J* = 8.2Hz, 1H), 7.45(dd, *J*
25 = 1.7, 9.1Hz, 1H), 7.51(dd, *J* = 1.5, 8.2Hz, 1H).

26 2-Fluoro-4-iodo-phenyl acetic acid (Intermediate 3)

27 A solution of 2-fluoro-4-iodo-phenyl acetonitrile (**Intermediate 2**,
28 2.05g, 7.83mmol) in ethanol (50mL and water (15mL) was treated with
29 potassium hydroxide (3.4g, 60.7mmol) and refluxed for 4h. The volatiles were

1 distilled off in *vacuo* and the residue was diluted with water and poured into
2 cold, dilute hydrochloric acid and the precipitated solid was filtered. The solid
3 was dissolved in diethyl ether, and the organic solution was dried over
4 anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to afford the
5 title compound a pale yellow solid (1.75g, 79%).
6 ¹H-NMR (300 MHz, CDCl₃): δ 3.64 (s, 2H), 6.98(t, *J* = 7.9Hz, 1H), 7.25-7.46
7 (m, 2H), 9.60-10.40(br s, 1H).

8 Ethyl-2-fluoro-4-iodo-phenyl acetate (Reagent C)

9 A solution of 2-fluoro-iodo-phenyl acetic acid (Intermediate 3, 1.75g,
10 6.22mmol) in ethanol (50mL) and benzene (100mL) was treated with
11 concentrated sulfuric acid (1.4mL) and heated at reflux overnight using a
12 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the
13 residue was diluted with water and diethyl ether. The phases were separated
14 and the organic phase was washed with saturated aqueous sodium bicarbonate
15 (x1), water (x1) and brine (x1), dried over anhydrous magnesium sulfate,
16 filtered and evaporated in *vacuo* to afford an oil which was subjected to flash
17 column chromatography over silica gel (230-400 mesh) using 5%-10% ethyl
18 acetate in hexane as the eluent to afford the title compound as a pale yellow
19 solid (1.4g, 73%).

20 ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, *J* = 7.1Hz, 3H), 3.60 (s, 2H), 4.16 (q, *J*
21 = 7.1Hz, 2H), 6.99(t, *J* = 8.0Hz, 1H), 7.39-7.44(m, 2H).

22 Methyl-2-fluoro-4-iodo-phenyl acetate (Reagent H)

23 A solution of 2-fluoro-4-iodo-phenyl acetonitrile (Intermediate 2, 3g,
24 11.45mmol) in methanol (50mL) and benzene (50mL) was treated with *p*-
25 toluene sulfonic acid (2.5g, 13.15mmol) and heated at reflux overnight using a
26 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the
27 residue was diluted with water and diethyl ether. The phases were separated
28 and the organic phase was washed with saturated aqueous sodium bicarbonate
29 (x1), water (x1) and brine (x1), dried over anhydrous magnesium sulfate,

1 filtered and evaporated in *vacuo* to afford an oil which was subjected to flash
2 column chromatography over silica gel (230-400 mesh) using 6% ethyl acetate
3 in hexane as the eluent to afford the title compound as a colorless oil (2.7g,
4 80%).

5 ¹H-NMR (300 MHz, CDCl₃): δ 3.62 (s, 2H), 3.70 (s, 3H), 6.99(t, *J* = 7.9Hz,
6 1H), 7.39-7.45(m, 2H).

7 GENERAL PROCEDURE A: 7-Methoxy-1,1-dimethyl-1,2,3,4-
8 tetrahydronaphthalene (Intermediate 8)

9 A stirred, cooled (-40°C) solution of titanium tetrachloride in anhydrous
10 dichloromethane (1M, 20mL) under argon, was treated with a solution of
11 dimethyl zinc (2M, 40mL) in toluene. After 0.5h, a solution of 7-methoxy-1-
12 tetralone (1.76g, 10mmol) in anhydrous dichloromethane (5mL) was
13 cannulated into the reaction mixture and the resulting solution was allowed to
14 warm to ambient temperature and stirred overnight. The reaction mixture was
15 then cooled to -40°C and cautiously quenched with methanol (11mL). It was
16 diluted with dichloromethane and saturated aqueous ammonium chloride
17 solution. The phases were separated and the aqueous phase was extracted with
18 dichloromethane (x2mL). The combined organic phase was dried over
19 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to the title
20 compound (1.75g, 92%) as an oil.

21 ¹H-NMR (300 MHz, CDCl₃): δ 1.33(s, 6H), 1.67-1.71(m, 2H), 1.79-1.90(m,
22 2H), 2.75(t, *J* = 6.2Hz, 2H), 3.83(s, 3H), 6.72(dd, *J* = 2.6, 8.3Hz, 1H), 6.93(d,
23 *J* = 2.6Hz, 1H), 7.02(d, *J* = 8.3Hz, 1H).

24 GENERAL PROCEDURE B: 6-Methoxy-4,4-dimethyl-1,2,3,4-
25 tetrahydronaphthalene-1-one (Intermediate 9)

26 A solution of 7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene
27 (Intermediate 8, 1.65g, 8.7 mmol) in 7.5mL of glacial acetic acid was cooled
28 to 0°C and treated with a solution of chromium trioxide (2g, 20mmol) in 8mL
29 of acetic acid and 7mL of water. The reaction mixture was then allowed to

1 warm to ambient temperature and stirred overnight. It was diluted with water
2 and extracted with diethyl ether (x2). The combined organic phase was
3 washed with water (x1), saturated aqueous sodium bicarbonate (x1) and brine
4 (x1), dried over anhydrous magnesium sulfate, filtered and evaporated in
5 *vacuo* to afford the title compound (1.64g, 93%) as a yellow oil.
6 ¹H-NMR (300 MHz, CDCl₃): δ 1.34(s, 6H), 1.96(t, *J* = 7.1Hz, 2H), 2.64(t, *J* =
7 7.1Hz, 2H), 3.83(s, 3H), 6.77(dd, *J* = 2.6, 8.7Hz, 1H), 6.83(d, *J* = 2.5Hz, 1H),
8 7.98(d, *J* = 8.7Hz, 1H).

9 6-Hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene-1-one (Intermediate
10 10)

11 A stirred, cooled (-78°C) solution of 6-methoxy-4,4-dimethyl-1,2,3,4-
12 tetrahydronaphthalene-1-one (Intermediate 9, 0.8, 3mmol) under argon was
13 treated with a 1M solution of boron tribromide (10mL). The reaction mixture
14 was allowed to warm to ambient temperature and stirred overnight. The
15 reaction mixture was cooled to -78°C, quenched and diluted with saturated
16 aqueous sodium bicarbonate solution and the aqueous phase was extracted
17 with dichloromethane (x2). The combined organic phase was dried over
18 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash
19 column chromatography over silica gel (230-400 mesh) using 30% ethyl
20 acetate in hexane as the eluent afforded the title compound (0.3g, 52%) as a
21 yellow viscous oil.

22 ¹H-NMR (300 MHz, CDCl₃): δ 1.33(s, 6H), 1.97(t, *J* = 6.8Hz, 2H), 2.71(t, *J* =
23 6.7Hz, 2H), 6.81(dd, *J* = 2.3, 8.5Hz, 1H), 6.94(d, *J* = 2.3Hz, 1H), 7.98(d, *J* =
24 8.7Hz, 1H), 9.35(s, 1H).

25 GENERAL PROCEDURE C: 4,4-Dimethyl-6-trifluoromethylsulfonyloxy-
26 1,2,3,4-tetrahydronaphthalene-1-one (Intermediate 11)

27 A stirred, cooled (0°C) solution of 6-hydroxy-4,4-dimethyl-1,2,3,4-
28 tetrahydronaphthalene-1-one (Intermediate 10, 0.3g, 1.6mmol) in anhydrous
29 dichloromethane (10mL) was treated with 4-(dimethylamino)pyridine (0.36g,

1 3.27mmol) followed by 2-[N,N'-bis(trifluoromethylsulfonyl)amino]-5-
2 chloropyridine (0.79g, 2mmol). After stirring at ambient temperature for
3 0.75h, the reaction mixture was diluted with dichloromethane and washed with
4 water (x1). The organic phase was dried over anhydrous sodium sulfate,
5 filtered and evaporated in *vacuo* to an oil. Flash column chromatography over
6 silica gel (230-400 mesh) using 8-10% ethyl acetate in hexane as the eluent
7 afforded the title compound (0.462g, 90%) as an off-white solid.
8 ¹H-NMR (300 MHz, CDCl₃): δ 1.36(s, 6H), 2.01(t, *J* = 6.8Hz, 2H), 2.70(t, *J* =
9 6.7Hz, 2H), 7.15(dd, *J* = 2.5, 8.7Hz, 1H), 7.28(d, *J* = 2.4Hz, 1H), 8.06(d, *J* =
10 8.7Hz, 1H).

11 GENERAL PROCEDURE D: 4,4-Dimethyl-6-trimethylsilanyl-ethynyl-
12 1,2,3,4-tetrahydronaphthalene-1-one (Intermediate 12)

13 A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-
14 tetrahydronaphthalene-1-one (Intermediate 11, 0.46g, 1.43mmol) in triethyl
15 amine (3mL) and anhydrous tetrahydrofuran (8mL) was treated with
16 copper(I)iodide (0.1g, 0.53mmol) and sparged with argon for 5 minutes.
17 Trimethylsilyl acetylene (0.85mL, 6mmol) was then added followed by
18 dichlorobis(triphenylphosphine)palladium(II) (0.25g, 0.36mmol). The
19 resulting reaction mixture was heated at 70°C for 17h. It was then cooled to
20 ambient temperature, diluted with diethyl ether and filtered over a bed of
21 celite. The filtrate was evaporated *vacuo* to an oil which was subjected to
22 flash column chromatography over silica gel (230-400 mesh) using 5% ethyl
23 acetate in hexane as the eluent to afford the title compound (0.28g, 72%).
24 ¹H-NMR (300 MHz, CDCl₃): δ 0.26(s, 9H), 1.36(s, 6H), 1.99(t, *J* = 6.8Hz,
25 2H), 2.69(t, *J* = 6.7Hz, 2H), 7.35(dd, *J* = 1.7, 8.2Hz, 1H), 7.49 (unresolved d,
26 1H), 7.93(d, *J* = 8.1Hz, 1H).

27 GENERAL PROCEDURE E: 6-Ethynyl-4,4-dimethyl-1,2,3,4-
28 tetrahydronaphthalene-1-one (Intermediate 13)

1 A solution of 4,4-dimethyl-6-trimethylsilanylethynyl-1,2,3,4-
2 tetrahydronaphthalene-1-one (**Intermediate 12**, 0.28g, 1.03mmol) in methanol
3 (10mL) was treated with potassium carbonate (0.74g, 5.35mmol) and stirred at
4 ambient temperature for 4h. The volatiles were distilled off in *vacuo* and the
5 residue was diluted with water and extracted with diethyl ether (x2). The
6 combined organic extract was dried over anhydrous magnesium sulfate,
7 filtered and evaporated in *vacuo* to afford the title compound (0.19g, 89%) as
8 an oil that solidified on standing.
9 ¹H-NMR (300 MHz, CDCl₃): δ 1.33(s, 6H), 1.96(t, *J* = 6.8Hz, 2H), 2.67(t, *J* =
10 6.8Hz, 2H), 3.25(s, 1H), 7.33(dd, *J* = 1.5, 8.1Hz, 1H), 7.49 (d, *J* = 1.5Hz,
11 1H), 7.13(d, *J* = 8.1Hz, 1H).

12 GENERAL PROCEDURE F: 4-(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-
13 naphthalene-2-yl-ethynyl)-benzoic acid ethyl ester (**Intermediate 14**)

14 A solution of 6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene-1-
15 one (**Intermediate 13**, 0.23g, 1.1mmol) and ethyl-4-iodo benzoate (**Reagent**
16 **A**, 0.36g, 1.3mmol) in triethyl amine (7mL) and anhydrous tetrahydrofuran
17 (3mL) was treated with copper(I)iodide (0.114g, 0.6mmol) and sparged with
18 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (0.23g,
19 0.33mmol) was added and the reaction mixture was stirred overnight at room
20 temperature. It was diluted with diethyl ether and filtered over a bed of celite.
21 The filtrate was evaporated in *vacuo* to a brown oil that was subjected to flash
22 column chromatography over silica gel (230-400 mesh) using 6-7% ethyl
23 acetate in hexane as the eluent to afford the title compound (0.29g, 72%) as a
24 pale brown solid.
25 ¹H-NMR (300 MHz, CDCl₃): δ 1.3(t, *J* = 7.1Hz, 3H), 1.37(s, 6H), 1.80 (t, *J* =
26 6.8Hz, 2H), 2.69(t, *J* = 6.8Hz, 2H), 4.35(q, *J* = 7.1Hz, 2H), 7.40(dd, *J* = 1.5,
27 8.2Hz, 1H), 7.51 (d, *J* = 1.6Hz, 1H), 7.57 (d, *J* = 8.3Hz, 2H), 7.96(d, *J* =
28 8.2Hz, 1H), 7.99(d, *J* = 8.5Hz, 2H).

1 GENERAL PROCEDURE G 4-(5-Cyclopropylamino-8,8-dimethyl-5,6,7,8-
2 tetrahydro-naphthalene-2-yl-ethynyl)-benzoic acid ethyl ester (Compound 1,
3 **General Formula 4)**

4 A solution of 4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-
5 ylethynyl)-benzoic acid ethyl ester (**Intermediate 14**, 0.14g, 0.4mmol) in 3mL
6 of dichloromethane and 2mL of acetonitrile was treated with cyclopropyl
7 amine(1mL, 14.45mmol). After 5 minutes, acetic acid (1mL) was added
8 followed by sodium cyanoborohydride (0.13g, 2mmol). The reaction was
9 stirred overnight at ambient temperature. It was then diluted with water and
10 saturated aqueous sodium carbonate solution and extracted with
11 dichloromethane (x2). The combined organic extract was dried over
12 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash
13 column chromatography over silica gel (230-400 mesh) using 20% ethyl
14 acetate in hexane as the eluent afforded the title compound (0.1g, 62%) as a
15 pale yellow solid.

16 ¹H-NMR (300 MHz, CDCl₃): δ 0.30-0.60(m, 4H), 1.28(s, 3H), 1.35 (s, 3H),
17 1.30(t, *J* = 7.1Hz, 3H), 1.55-1.61(m, 1H), 1.83-2.05(m, 3H), 2.25 (quintet, *J* =
18 3.0 Hz, 1H), 3.80 (t, *J* = 4.9Hz, 1H), 4.39(q, *J* = 7.1Hz, 2H), 7.27-7.36(m,
19 2H), 7.52 (s, 1H), 7.55(d, *J* = 8.3Hz, 2H), 8.03(d, *J* = 8.5Hz, 2H).

20 GENERAL PROCEDURE H 4-[(5-Cyclopropyl-methyl-amino)-8,8-dimethyl-
21 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-benzoic acid ethyl ester
22 **(Compound 2, General Formula 4)**

23 A solution of 4-(5-cyclopropylamino-8,8-dimethyl-5,6,7,8-tetrahydro-
24 naphthalene-2-ylethynyl)-benzoic acid ethyl ester (**Compound 1**, 0.064g,
25 0.16mmol) in acetone (2mL) was treated with potassium carbonate (0.6g,
26 4.34mmol) and methyl iodide (1mL, 16mmol) and stirred overnight at ambient
27 temperature. The volatiles were distilled off in *vacuo* and the residue was
28 diluted with water and extracted with dichloromethane (x2). The combined

1 organic extract was dried over anhydrous sodium sulfate, filtered and
2 evaporated in *vacuo* to afford the title compound (0.065g, 99%).
3 ¹H-NMR (300 MHz, CDCl₃): δ 0.28-0.49 (m, 4H), 1.21(s, 3H), 1.26 (s, 3H),
4 1.33 (t, *J* = 7.1Hz, 3H), 1.58-1.73 (m, 2H), 1.83-1.89 (m, 2H), 2.02-2.08 (m,
5 1H), 2.06 (s, 3H), 3.88 (t, *J* = 8.1Hz, 1H), 4.32(q, *J* = 7.1Hz, 2H), 7.20(d, *J* =
6 7.8Hz, 1H), 7.41 (s, 1H), 7.46 (d, *J* = 7.8Hz, 1H), 7.52(d, *J* = 8.4Hz, 2H),
7 8.03(d, *J* = 8.3Hz, 2H).

8 GENERAL PROCEDURE I: 4-[(5-Cyclopropyl-methyl-amino)-8,8-dimethyl-
9 5,6,7,8-tetrahydro-naphthalene-2yl-ethynyl]-benzoic acid (Compound 3,
10 **General Formula 4**) A solution of 4-[(5-cyclopropyl-methyl-amino)-8,8-
11 dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-benzoic acid ethyl ester
12 (Compound 2, 0.065g, 0.158mmol) in ethanol (1mL) and tetrahydrofuran
13 (1mL) was treated with 1M aqueous sodium hydroxide solution (1mL) and
14 heated at 80°C for 1h. The volatiles were distilled off in *vacuo* and the residue
15 was diluted with saturated aqueous ammonium chloride solution and extracted
16 with ethyl acetate (x2). The combined organic extract was dried over
17 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford a solid
18 that was washed with dichloromethane and dried to afford the title compound
19 (0.029g, 38%) as a white solid.

20 ¹H-NMR (300 MHz, CD₃COCD₃): δ 0.35-0.51(m, 4H), 1.26(s, 3H), 1.29 (s,
21 3H), 1.60-1.82(m, 2H), 1.88-2.02(m, 2H), 2.02-2.15 (m, 1H), 2.10 (s, 3H),
22 3.93 (t, *J* = 8.0Hz, 1H), 7.26(dd, *J* = 1.5, 8.2Hz, 1H), 7.51 (d, *J* = 1.5Hz, 1H),
23 7.52(d, *J* = 8.2Hz, 1H), 7.62(d, *J* = 8.5Hz, 2H), 8.02(d, *J* = 8.2Hz, 2H).
24 4-[(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-
25 acetic acid methyl ester (Compound 4, General Formula 8)

26 Following general procedure F and using 6-ethynyl-4,4-dimethyl-
27 1,2,3,4-tetrahydronaphthalene-1-one (Intermediate 13, 0.312g, 1.5mmol), 4-
28 iodo phenyl acetic acid methyl ester (Reagent B, 0.50g, 1.8mmol), triethyl
29 amine (7mL), anhydrous tetrahydrofuran (3mL), copper(I)iodide (0.04g,

1 0.2mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.15g,
2 0.213mmol) followed by flash column chromatography over silica gel (230-
3 400 mesh) using 16-20% ethyl acetate in hexane as the eluent, the title
4 compound was obtained as a pale yellow solid (0.42g, 76%).
5 ¹H-NMR (300 MHz, CDCl₃): δ 1.42(s, 6H), 2.04(t, *J* = 6.7Hz, 2H), 2.74(t, *J* =
6 6.7Hz, 2H), 3.66(s, 2H), 3.71(s, 3H), 7.29 (d, *J* = 8.2Hz, 2H), 7.43(dd, *J* = 1.5,
7 7.9Hz, 1H), 7.52 (d, *J* = 8.2Hz, 2H), 7.57 (d, *J* = 1.5Hz, 1H), 8.00(d, *J* =
8 8.2Hz, 1H).

9 GENERAL PROCEDURE J: 4-[(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-
10 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid (Compound 5, General
11 Formula 8)

12 A solution of 4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-
13 2-ylethynyl)-phenyl]-acetic acid methyl ester (Compound 4, 0.1g, 0.28mmol)
14 in a mixture of methanol (2mL), tetrahydrofuran (3.5mL) and water (1.5mL)
15 was treated with lithium hydroxide monohydrate (0.11g, 2.62mmol) and the
16 resulting reaction mixture was stirred at ambient temperature for 3h. The
17 volatiles were distilled off in *vacuo* and the residue was diluted with water and
18 dilute hydrochloric acid and extracted with ethyl acetate (x3). The combined
19 organic phase was dried over anhydrous sodium sulfate, filtered and
20 evaporated in *vacuo* to afford the title compound as a pale yellow solid
21 (0.088g, 92%).

22 ¹H-NMR (300 MHz, CDCl₃): δ 1.41(s, 6H), 2.02(t, *J* = 6.7Hz, 2H), 2.74(t, *J* =
23 6.8Hz, 2H), 3.68(s, 2H), 7.28 (d, *J* = 8.2Hz, 2H), 7.42(dd, *J* = 1.5, 8.2Hz, 1H),
24 7.52 (d, *J* = 8.2Hz, 2H), 7.56 (d, *J* = 1.5Hz, 1H), 7.99(d, *J* = 8.2Hz, 1H).

25 4-[(5-(Cyclopropyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-yl-
26 ethynyl)-phenyl]-acetic acid methyl ester (Compound 6, General Formula
27 4)

28 Following general procedure G and using 4-[(8,8-dimethyl-5-oxo-
29 5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid methyl ester

1 (Compound 4, 0.2g, 0.54mmol), dichloromethane (4mL), acetonitrile(2mL),
2 cyclopropyl amine(1mL, 14.45mmol), acetic acid (1mL)and sodium
3 cyanoborohydride (0.16g, 2.54mmol) followed by flash column
4 chromatography over silica gel (230-400 mesh) using 30% ethyl acetate in
5 hexane as the eluent the title compound was obtained as a pale yellow oil
6 (0.22g, 99%).

7 ¹H-NMR (300 MHz, CDCl₃): δ 0.38-0.60 (m, 4H), 1.26(s, 3H), 1.33(s, 3H),
8 1.50-1.59(m, 1H), 1.79-2.10 (m, 3H), 2.25(m, 1H), 3.63(s, 2H), 3.69(s, 3H),
9 3.79(t, *J* = 4.8Hz, 1H), 7.20-7.32 (m, 4H), 7.47(s, 1H), 7.58(d, *J* = 8.2Hz, 2H).

10 4-[(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-
11 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid methyl ester (Compound 7,
12 **General Formula 4)**

13 Following general procedure H and using 4-[(5-(cyclopropyl-amino)-
14 8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-phenyl]-acetic acid
15 methyl ester (Compound 6, 0.15g, 0.37mmol), acetone (5mL), potassium
16 carbonate (1.1g, 7.95mmol) and methyl iodide (1mL, 16mmol), the following
17 work-up was used. The volatiles were distilled off in *vacuo* and the residue
18 was diluted with water and extracted with dichloromethane (x2). The
19 combined organic extract was dried over anhydrous sodium sulfate, filtered
20 and evaporated in *vacuo* to afford the title compound (0.148g, 97%).

21 ¹H-NMR (300 MHz, CDCl₃): δ 0.38-0.58(m, 4H), 1.27(s, 3H), 1.31 (s, 3H),
22 1.68-1.81(m, 2H), 1.85-1.98(m, 2H), 2.08-2.15 (m, 1H), 2.12 (s, 3H), 3.62(s,
23 2H), 3.69(s, 3H), 3.94 (t, *J* = 7.9Hz, 1H), 7.24(d, *J* = 8.2Hz, 1H), 7.24 (d, *J* =
24 8.2Hz, 2H), 7.44-7.51(m, 4H).

25 4-[(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-
26 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid (Compound 8, General
27 **Formula 4)**

28 Following general procedure J and using 4-[(5-(cyclopropyl-methyl-
29 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2ylethynyl)-phenyl]-

1 acetic acid methyl ester (**Compound 7**, 0.148g, 0.357mmol), methanol (2mL),
2 tetrahydrofuran (4mL), water (1mL) and lithium hydroxide monohydrate
3 (0.25g, 5.95mmol) followed by flash column chromatography over silica gel
4 (230-400 mesh) using 30-75% ethyl acetate in hexane as the eluent, the title
5 compound was obtained as a white solid (0.08g, 56%).
6 ¹H-NMR (300 MHz, CDCl₃): δ 0.52-0.54(m, 2H), 0.68-0.70(m, 2H), 1.27(s,
7 3H), 1.29(s, 3H), 1.63-1.80(m, 2H), 1.95-2.17(m, 2H), 2.19-2.24(m, 1H),
8 2.24(s, 3H), 3.60(s, 2H), 4.18(t, *J* = 7.7Hz, 1H), 7.24(dd, *J* = 1.5, 8.2Hz, 1H),
9 7.26 (d, *J* = 8.2Hz, 2H), 7.43 (d, *J* = 8.2Hz, 1H), 7.47(s, 1H), 7.47(d, *J* =
10 8.2Hz, 2H), 10.37(br s, 1H).

11 2-Fluoro-4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-
12 ethynyl)]benzoic acid ethyl ester (**Compound 9**, General Formula 8)

13 A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-
14 tetrahydronaphthalene-1-one (**Intermediate 11**, 0.3g, 0.9mmol),
15 copper(I)iodide (0.057g, 0.3mmol) and ethyl-2-fluoro-4-ethynyl-benzoate
16 (**Reagent D**, 0.44g, 2.27mmol) in triethyl amine (2mL) and tetrahydrofuran
17 (3mL) was sparged with argon for 5 minutes and treated with
18 dichlorobis(triphenylphosphine)palladium(II) (0.135g, 0.192mmol) and stirred
19 at room temperature overnight and then refluxed for 2h. It was then cooled to
20 ambient temperature, diluted with diethyl ether and filtered over a bed of
21 celite. The filtrate was evaporated in *vacuo* to an oil which was subjected to
22 flash column chromatography over silica gel (230-400 mesh) using 10-15%
23 ethyl acetate in hexane as the eluent to afford the title compound as a yellow
24 solid (0.22g, 67%).

25 ¹H-NMR (300 MHz, CDCl₃): δ 1.38 (t, *J* = 7.0Hz, 3H), 1.39(s, 6H), 2.01(t, *J*
26 = 6.7Hz, 2H), 2.71(t, *J* = 6.7Hz, 2H), 4.37(q, *J* = 7Hz, 2H), 7.28(dd, *J* = 0.9,
27 10Hz, 1H), 7.34(dd, *J* = 0.9, 8.2Hz, 1H), 7.41 (dd, *J* = 1.5, 8.2Hz, 1H), 7.57(d,
28 *J* = 0.9Hz), 7.90(t, *J* = 7.9Hz, 1H), 7.93 (d, *J* = 7.9Hz, 1H).

1 2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
2 benzoic acid (Compound 10, General Formula 8)

3 A solution of 2-fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-
4 naphthalen-2-ylethynyl)benzoic acid ethyl ester (Compound 9, 0.1g,
5 0.274mmol) in ethanol(4mL), methanol (2mL) and tetrahydrofuran (2mL) was
6 treated with 1M aqueous sodium hydroxide solution and heated at 70°C for
7 1h. The volatiles were distilled off in *vacuo* and the residue was diluted with
8 water and dilute hydrochloric acid and extracted with ethyl acetate (x2). The
9 combined organic extract was dried over anhydrous sodium sulfate, filtered
10 and evaporated in *vacuo* to afford a solid that was recrystallized from hot
11 aqueous acetonitrile to afford the title compound (0.025g, 27%).

12 ¹H-NMR (300 MHz, CDCl₃): δ 1.43(s, 6H), 2.05(t, *J* = 6.9Hz, 2H), 2.76(t, *J* =
13 6.9Hz, 2H), 7.26-7.47(m, 3H), 7.60(d, *J* = 1.1Hz, 1H), 7.99-8.05(m, 2H).

14 4-[5-(Cyclopropyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-
15 ethynyl]-2-fluoro-benzoic acid ethyl ester (Compound 11, General Formula
16 4)

17 Following general procedure G and using 2-fluoro-4-(8,8-dimethyl-5-
18 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-benzoic acid ethyl ester
19 (Compound 9, 0.132g, 0.3mmol), dichloromethane (4mL), acetonitrile(2mL),
20 cyclopropyl amine(1mL, 14.45mmol), acetic acid (1mL)and sodium
21 cyanoborohydride (0.18g, 2.86mmol) followed by flash column
22 chromatography over silica gel (230-400 mesh) using 16-20% ethyl acetate in
23 hexane as the eluent, the title compound was obtained as a pale yellow oil
24 (0.1g, 82%).

25 ¹H-NMR (300 MHz, CDCl₃):δ 0.36-0.54 (m, 4H), 1.27(s, 3H), 1.33(s, 3H),
26 1.40(t, *J* = 7.0Hz, 3H), 1.54-1.61(m, 2H), 1.82-2.05 (m, 2H), 2.26(m, 1H),
27 3.79 (t, *J* = 4.9Hz, 1H), 4.39(q, *J* = 7.1Hz, 2H), 7.26-7.50(m, 4H), 7.87(s, 1H),
28 7.92 (t, *J* = 7.9Hz, 1H).

1 4-[5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-
2 naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid ethyl ester (Compound 12,
3 **General Formula 4)**

4 Following general procedure H and using 4-[5-(cyclopropyl-methyl-
5 amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-2-fluoro-
6 benzoic acid ethyl ester (**Compound 11**, 0.1g, 0.246mmol), acetone (4mL),
7 potassium carbonate (0.917g, 6.63mmol) and methyl iodide (0.8mL, 11mmol),
8 the following work-up was used. The volatiles were distilled off in *vacuo* and
9 the residue was diluted with water and extracted with dichloromethane (x2).
10 The combined organic extract was dried over anhydrous sodium sulfate,
11 filtered and evaporated in *vacuo* to an oil. Flash column chromatography over
12 silica gel (230-400 mesh) using 8-10% ethyl acetate in hexane as the eluent
13 afforded the title compound as a pale yellow oil (0.102g, 98%).
14 ¹H-NMR (300 MHz, CDCl₃): δ 0.39-0.62 (m, 4H), 1.29(s, 3H), 1.34(s, 3H),
15 1.42(t, *J* = 6.9Hz, 3H), 1.65-1.82(m, 2H), 1.85-2.02 (m, 2H), 2.02-2.10(m,
16 1H), 2.15(s, 3H), 3.97(t, *J* = 7.7Hz, 1H), 4.42(q, *J* = 7.0Hz, 2H), 7.28-7.36 (m,
17 3H), 7.59(s, 1H), 7.55(d, *J* = 7.9Hz, 2H), 7.92 (t, *J* = 7.5Hz, 1H).
18 4-[5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-
19 naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid (Compound 13, General
20 **Formula 4)**

21 Following general procedure I and using 4-[(5-cyclopropyl-methyl-
22 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-2-fluoro-
23 benzoic acid ethyl ester (**Compound 12**, 0.102g, 0.23mmol), ethanol (4mL)
24 and 1M aqueous sodium hydroxide solution (2mL) followed by flash column
25 chromatography over silica gel (230-400 mesh) 30% ethyl acetate in hexane as
26 the eluent, the title compound was obtained as an off-white solid(0.015g,
27 16%).
28 ¹H-NMR (300 MHz, CDCl₃): δ 0.54-0.65 (m, 4H), 1.29 (s, 3H), 1.32 (s, 3H),
29 1.68-1.83 (m, 2H), 1.97-2.05 (m, 2H), 2.18-2.25 (m, 1H), 2.25 (s, 3H), 4.13 (t,

1 $J = 6.7\text{Hz}$, 1H), 7.26-7.30 (m, 2H), 7.34 (dd, $J = 1.5$, 7.9Hz, 1H), 7.48 (d, $J =$
2 1.8Hz, 1H), 7.60 (d, $J = 8.5\text{Hz}$, 1H), 7.95 (t, $J = 7.9\text{Hz}$, 1H).

3 [2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl)-
4 ethynyl]-phenyl]acetic acid ethyl ester (**Compound 14**, General Formula 8)

5 Following general procedure F and using 6-ethynyl-4,4-dimethyl-
6 1,2,3,4-tetrahydro-naphthalene-1-one (**Intermediate 13**, 0.298g, 1.43mmol),
7 2-fluoro-4-iodo phenyl acetic acid ethyl ester (**Reagent C**, 0.44g, 1.43mmol),
8 triethyl amine (**Intermediate 13**, 3mL), anhydrous tetrahydrofuran (7mL),
9 copper(I)iodide (0.04g, 0.2mmol) and
10 dichlorobis(triphenylphosphine)palladium(II) (0.15g, 0.213mmol) followed by
11 flash column chromatography over silica gel (230-400 mesh) using 14-16%
12 ethyl acetate in hexane as the eluent, the title compound was obtained as an oil
13 (0.43g, 77%).

14 $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.26(t, $J = 7.2\text{Hz}$, 3H), 1.41(s, 6H), 2.04(t, $J =$
15 6.7Hz, 2H), 2.74(t, $J = 6.7\text{Hz}$, 2H), 3.68(s, 2H), 4.18(q, $J = 7.1\text{Hz}$, 2H), 7.23-
16 7.57(m, 4H), 7.59 (d, $J = 1.5\text{Hz}$, 1H), 7.99(d, $J = 7.9\text{Hz}$, 1H).

17 [2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl)-
18 ethynyl]phenyl]-acetic acid (**Compound 15**, General Formula 8)

19 Following general procedure J and using [2-fluoro-4-(8,8-dimethyl-5-
20 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)phenyl]acetic acid methyl
21 ester (**Compound 14**, 0.18g, 0.48mmol), methanol (4mL), tetrahydrofuran
22 (8mL), water (2mL) and lithium hydroxide monohydrate (0.2g, 4.76mmol)
23 followed by flash column chromatography over silica gel (230-400 mesh)
24 using 50- 100% ethyl acetate in hexane as the eluent, the title compound was
25 obtained as a dirty white solid (0.068g, 41%).

26 $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.41(s, 6H), 2.03(t, $J = 6.7\text{Hz}$, 2H), 2.74(t, $J =$
27 6.8Hz, 2H), 3.73(s, 2H), 7.24-7.32(m, 3H), 7.42(dd, $J = 1.5$, 7.9Hz, 1H), 7.56
28 (s, 1H), 7.99(d, $J = 7.9\text{Hz}$, 1H), 9.40-10.00 (br s, 1H).

1 [4-(5-(Cyclopropyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-
2 ethynyl)-2-fluoro-phenyl] acetic acid ethyl ester (Compound 16, General
3 **Formula 4)**

4 Following general procedure G and using [2-fluoro-4-(8,8-dimethyl-5-
5 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl) phenyl]acetic acid ethyl ester
6 (**Compound 14**, 0.258g, 0.68mmol), dichloromethane (4mL),
7 acetonitrile(2mL), cyclopropyl amine(1mL, 14.45mmol), acetic acid (1mL)and
8 sodium cyanoborohydride (0.266g, 4.23mmol) followed by flash column
9 chromatography over silica gel (230-400 mesh) using 16-20-25% ethyl acetate
10 in hexane as the eluent, the title compound was obtained as a pale yellow oil
11 (0.21g, 73%).

12 ¹H-NMR (300 MHz, CDCl₃):δ 0.35-0.54 (m, 4H), 1.25(t, *J* = 7.1Hz, 3H),
13 1.26(s, 3H), 1.32(s, 3H), 1.53-1.64(m, 1H), 1.82-2.05 (m, 3H), 2.21-2.28(m,
14 1H), 3.65(s, 2H), 3.78(t, *J* = 5.0Hz, 1H), 4.17(q, *J* = 7.1Hz, 2H), 7.19-7.41 (m,
15 5H), 7.47(d, *J* = 1.5Hz, 1H).

16 [4-(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-
17 naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid ethyl ester
18 (**Compound 17, General Formula 8)**

19 Following general procedure H and using [4-((5-cyclopropyl-amino)-
20 8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2ylethynyl)-2-fluoro-
21 phenyl]acetic acid ethyl ester (**Compound 16**, 0.21g, 0.5mmol), acetone
22 (5mL), potassium carbonate (1.13g, 8.17mmol) and methyl iodide (0.5mL,
23 8mmol), the following work-up was used. The volatiles were distilled off in
24 *vacuo* and the residue was diluted with water and extracted with
25 dichloromethane (x2). The combined organic extract was dried over
26 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford an oil.
27 Flash column chromatography over silica gel (230-400 mesh) using 8% ethyl
28 acetate in hexane as the eluent afforded the title compound (0.15g, 69%).

¹H-NMR (300 MHz, CDCl₃): δ 0.39-0.53(m, 4H), 1.27(s, 3H), 1.31 (s, 3H),
1.66-1.81(m, 2H), 1.89-2.05(m, 2H), 2.08-2.13 (m, 1H), 2.13 (s, 3H), 3.62(s,
2H), 3.94 (t, *J* = 8.0Hz, 1H), 4.16(q, *J* = 7.1Hz, 2H), 7.20-7.29(m, 4H), 7.44(d,
J = 1.5Hz, 1H), 7.51 (d, *J* = 8.2Hz, 1H).

[4-(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-
naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid (Compound 18,
General Formula 4)

Following general procedure J and using [4-(5-(cyclopropyl-methyl-
amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-2-fluoro-
phenyl]-acetic acid ethyl ester (**Compound 17**, 0.025g, 0.059mmol), methanol
(1mL), tetrahydrofuran (1mL), water (0.5mL) and lithium hydroxide
monohydrate (0.060g, 1.43mmol), the title compound was obtained as a white
solid (0.023g, 95%).

¹H-NMR (300 MHz, CDCl₃):δ 0.52-0.54(m, 2H), 0.68-0.70(m, 2H), 1.27(s,
3H), 1.29(s, 3H), 1.63-1.80(m, 2H), 1.95-2.17(m, 2H), 2.19-2.24(m, 1H),
2.24(s, 3H), 3.60(s, 2H), 4.18(t, *J* = 7.7Hz, 1H), 7.19-7.28(m, 4H), 7.45 (d, *J*
= 1.5Hz, 1H), 7.49(d, *J* = 8.2Hz, 1H), 8.80-9.20(br s, 1H).

GENERAL PROCEDURE K: 8,8-Dimethyl-5,6,7,8-tetrahydro-naphthalene-1-
one-2-carboxylic acid-4-(tert-butoxycarbonylmethyl)phenyl ester Compound
19, General Formula 8)

A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-
tetrahydronaphthalene-1-one (**Intermediate 11**, 0.14g, 0.434mmol), *t*-butyl-4-
hydroxy-phenyl acetate (**Reagent E**, 0.14g, 0.673mmol), palladium acetate
(0.054g, 0.24mmol) and 1,3-bis(diphenylphosphino)propane (0.082g,
0.2mmol) in a mixture of dimethylsulfoxide (1mL), 1,2-dichloroethane
(1.5mL) and triethyl amine (1mL) was heated at 70°C under an atmosphere of
carbon monoxide overnight. The volatiles were distilled off in *vacuo* and the
residue was diluted with water and extracted with diethyl ether (x3). The
combined organic extract was dried over anhydrous magnesium sulfate,

1 filtered and evaporated in *vacuo* to an oil which was subjected to flash column
2 chromatography over silica gel (230-400 mesh) using 15% ethyl acetate in
3 hexane as the eluent to afford the title compound (0.11g, 53%).
4 ¹H-NMR (300 MHz, CDCl₃): δ 1.44(s, 3H), 1.44(s, 9H), 1.46 (s, 3H), 2.07(t, *J*
5 = 6.9Hz, 2H), 2.76(t, *J* = 6.8Hz, 2H), 3.55(s, 2H), 7.17 (d, *J* = 8.5Hz, 2H),
6 7.35(d, *J* = 8.5Hz, 2H), 8.05-8.13(m, 2H), 8.25 (d, *J* = 1.5Hz, 1H).

7 8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid-4-
8 (carboxymethyl)phenyl ester (Compound 20, General Formula 8)

9 A solution of 8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-
10 carboxylic acid 4-(*tert*-butoxycarbonylmethyl)phenyl ester (Compound 19,
11 0.11g, 0.229mmol) in dichloromethane (2mL) was treated with trifluoroacetic
12 acid (0.85mL and stirred at ambient temperature for 2.5h. The volatiles were
13 distilled off in *vacuo* and the residue was diluted with water and extracted with
14 ethyl acetate (x3). The combined organic phase was dried over anhydrous
15 sodium sulfate, filtered and evaporated in *vacuo* to afford a solid which was
16 subjected to flash column chromatography over silica gel (230-400 mesh)
17 using ethyl acetate as the eluent to afford the title compound (0.024g, 25%).
18 ¹H-NMR (300 MHz, CDCl₃): δ 1.46 (s, 6H), 2.08(t, *J* = 6.7Hz, 2H), 2.80(t, *J*
19 = 6.7Hz, 2H), 3.70(s, 2H), 7.20(d, *J* = 8.5Hz, 2H), 7.37(d, *J* = 8.5Hz, 2H),
20 8.08(dd, *J* = 1.4, 8.2Hz, 1H), 8.14 (d, *J* = 8.2Hz, 1H), 8.24 (d, *J* = 1.2Hz, 1H).

21 5-Methoxy-3,3-dimethyl-indane (Intermediate 15)

22 Following general procedure A and using titanium tetrachloride
23 (5.5mL, 50mmol), anhydrous dichloromethane (80mL), 2M solution dimethyl
24 zinc (50mL) in toluene and a solution of 6-methoxy-indane-1-one (4.05g,
25 25mmol) in dichloromethane (10mL) the title compound was obtained as an
26 oil (3.13g, 71%).
27 ¹H-NMR (300 MHz, CDCl₃): δ 1.37 (s, 6H), 2.04(t, *J* = 7.2Hz, 2H), 2.94(t, *J* =
28 7.2Hz, 2H), 3.89(s, 3H), 6.82(d, *J* = 2.1Hz, 1H), 7.28(dd, *J* = 2.1, 7.0Hz, 1H),
29 7.35 (d, *J* = 7.0Hz, 1H).

1 5-Methoxy-3,3-dimethyl-indane-1-one (Intermediate 16)

2 Following general procedure B and using 5-methoxy-3,3-dimethyl
3 indane (**Intermediate 15**, 3.13g, 17.78mmol) in 20mL of glacial acetic acid
4 and a solution of chromium trioxide (3.91g, 39.1mmol) in 20mL of acetic acid
5 and 20mL of water the title compound was obtained as a viscous yellow oil
6 (3.3g, 97%).

7 ¹H-NMR (300 MHz, CDCl₃): δ 1.37 (s, 6H), 2.54 (s, 2H), 3.87(s, 3H), 6.86-
8 6.87 (m, 2H), 7.60 (d, *J* = 7.0Hz, 1H).

9 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-1-one (Intermediate
10 17)

11 A solution of 5-methoxy-3,3-dimethyl-indane-1-one (**Intermediate 16**,
12 3.3g, 17.4mmol) in benzene (50mL) was treated with concentrated sulfuric
13 acid (10mL) and heated to 60°C. Sodium azide (1.95g, 30mmol) was added in
14 small portions and after the addition was complete, the reaction mixture was
15 heated further for 4h. It was then cooled, diluted with water and extracted with
16 chloroform (x3). The combined organic phase was dried over anhydrous
17 magnesium sulfate, filtered and evaporated in *vacuo* to afford the title
18 compound as a brown solid (3.5g, quantitative by weight).

19 ¹H-NMR (300 MHz, CDCl₃): δ 1.31 (s, 6H), 3.28 (s, 2H), 3.83(s, 3H), 6.78 (d,
20 *J* = 2.6Hz, 1H), 6.82(dd, *J* = 2.6Hz, 8.5Hz, 1H), 7.59 (s, 1H), 8.02 (d, *J* =
21 8.2Hz, 1H).

22 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline (Intermediate 18)

23 A solution of 6-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-
24 1-one (**Intermediate 17**, 3.5g, 17mmol) in 100mL of anhydrous
25 tetrahydrofuran was treated with lithium aluminum hydride (1.3g,
26 34.25mmol) in small portions and the resulting suspension was refluxed for 3
27 hours under argon. The reaction mixture was then cooled in an ice bath and
28 cautiously quenched with saturated aqueous sodium sulfate solution and the
29 resulting slurry was filtered and the filter-cake washed well with ethyl acetate.

1 The filtrate and washings were evaporated in *vacuo* to a brown oil which was
2 dissolved in chloroform, the solution was dried over anhydrous magnesium
3 sulfate, filtered and evaporated in *vacuo* to afford the title compound (3.2g,
4 ~100%).
5 ¹H-NMR (300 MHz, CDCl₃): δ 1.27 (s, 6H), 2.22 (s, 1H), 2.84 (s, 2H), 3.79 (s,
6 3H), 3.95 (s, 2H), 6.68(dd, *J* = 2.4Hz, 8.3Hz, 1H), 6.86(d, *J* = 2.4Hz, 1H), 6.91
7 (d, *J* = 8.3Hz, 1H).

8 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde
9 **(Intermediate 19)**

10 A solution of 6-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline
11 **(Intermediate 18, 3.2g, 16.7mmol)** in anhydrous dichloromethane (40mL)
12 was treated with formic acid (1mL, 26.5mmol) followed 1-(3-
13 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.9g, 20.34mmol)
14 and the resulting solution was stirred at ambient temperature overnight. It was
15 then diluted with chloroform and washed with water (x1) and brine (x1), dried
16 over anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to afford
17 the title compound as pale brown viscous oil (3.26g, 90%).
18 ¹H-NMR (300 MHz, CDCl₃): δ 1.28 (s, 6H), 3.32 (s, 0.7H), 3.54 (s, 0.3H),
19 3.79(s, 3H), 4.54 (s, 0.3H), 4.66(s, 0.7H), 6.71(dd, *J* = 2.6Hz, 8.2Hz, 1H),
20 6.85-6.97(m, 1H), 7.02-7.27(m, 1H), 8.15(s, 0.7H), 8.34(s, 0.3H), 8.40-8.80
21 (br s, 1H).

22 6-Hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde
23 **(Intermediate 20)** A stirred, cooled (-78°C) solution of 6-methoxy-4,4-
24 dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde **(Intermediate 19,**
25 **3.26g, 15mmol)** in anhydrous dichloromethane (15mL) was treated with 1M
26 solution of boron tribromide in dichloromethane (50mL) stirred at ambient
27 temperature for 3h. It was then cooled again to 78°C and quenched carefully
28 with saturated aqueous sodium carbonate solution, diluted with water and the
29 aqueous phase was extracted with ethyl acetate (x2). The combined organic

1 extract was dried over anhydrous sodium sulfate, filtered and evaporated in
2 *vacuo* to afford the title compound as a solid foam (3g, 99%).

3 ¹H-NMR (300 MHz, CDCl₃): δ 1.23 (s, 6H), 3.31 (s, 0.7H), 3.54 (s, 0.3H),
4 4.51 (s, 0.3H), 4.64 (s, 0.7H), 6.70-6.75(m, 1H), 6.84-6.90(m, 2H), 7.50-
5 7.80(br s, 1H), 8.12(s, 0.7H), 8.32(s, 0.3H).

6 2-Cyclopropyl-6-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline
7 **(Intermediate 21)**

8 A stirred, cooled (0°C) solution of 6-hydroxy-4,4-dimethyl-1,2,3,4-
9 tetrahydro-isoquinoline-2-carbaldehyde (**Intermediate 20**, 2.3g, 11.21mmol)
10 in anhydrous tetrahydrofuran (40mL) under argon was treated with titanium
11 tetra-*iso*-propoxide (8.28mL, 28mmol) followed by 3M solution of ethyl
12 magnesium bromide in diethyl ether (18.7mL) and the reaction mixture was
13 then heated at 55°C overnight. It was then cooled in an ice-bath, quenched
14 with saturated aqueous ammonium chloride solution and extracted with diethyl
15 ether (x2). The combined organic phase was dried over anhydrous sodium
16 sulfate, filtered and evaporated in *vacuo* to afford a yellow oily solid. Flash
17 column chromatography over silica gel (230-400 mesh) using 10-20% ethyl
18 acetate in hexane as the eluent afforded the title compound as a pale yellow
19 solid (1.55g, 63%).

20 ¹H-NMR (300 MHz, CD₃COCD₃): δ 0.016-0.16(m, 4H), 0.847 (s, 6H), 1.37
21 (m, 1H), 2.20(s, 2H), 3.25 (s, 2H), 6.22(dd, *J* = 2.4, 8.2Hz, 1H), 6.41(d, *J* =
22 2.6Hz, 1H), 6.47(d, *J* = 8.2Hz, 1H), 7.62(s, 1H).

23 2-Cyclopropyl-4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydro-
24 isoquinoline (**Intermediate 22**)

25 Following general procedure C and using 2-cyclopropyl-6-hydroxy-4,4-
26 dimethyl-1,2,3,4-tetrahydro-isoquinoline (**Intermediate 21**, 1.5g, 6.9mmol) in
27 anhydrous dichloromethane (30mL), triethyl amine (1.5mL, 10.39mmol) and
28 [N,N'-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (2.75g, 7mmol)
29 followed by flash column chromatography over silica gel (230-400 mesh)

1 using 8% ethyl acetate in hexane as the eluent the title compound was obtained
2 (2.23g, 92%) as oil. ¹H-NMR (300 MHz, CDCl₃): δ 0.42-0.54(m, 4H), 1.25(s,
3 6H), 1.76(m, 1H), 2.62(s, 2H), 3.74(s, 2H), 6.98(dd, *J* = 2.3, 8.4Hz, 1H),
4 7.16(d, *J* = 8.2Hz, 1H), 7.14(d, *J* = 2.3Hz, 1H).

5 Ethyl-2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-
6 carboxylate (Intermediate 23)

7 Following general procedure K and using 2-cyclopropyl-4,4-dimethyl-
8 6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydro-isoquinoline (Intermediate
9 22, 1.6g, 4.6mmol), palladium acetate (0.127g, 0.56mmol), 1,3-
10 bis(diphenylphosphino)propane (0.160g, 0.39mmol), dimethylsulfoxide
11 (2mL), 1,2-dichloroethane (5mL), triethyl amine (2mL), ethanol (5mL) and an
12 atmosphere of carbon monoxide followed by flash column chromatography
13 over silica gel (230-400 mesh) using 10% ethyl acetate in hexane as the eluent
14 the title compound was obtained as an oil (1g, 79%).

15 ¹H-NMR (300 MHz, CDCl₃):δ 0.44-0.54(m, 4H), 1.27(s, 6H), 1.38 (t, *J* =
16 7Hz, 3H), 1.73(m, 1H), 2.62(s, 2H), 3.76(s, 2H), 4.35 (q, *J* = 7.1Hz, 2H),
17 7.04(d, *J* = 7.9Hz, 1H), 7.74 (dd, *J* = 1.7, 7.9Hz, 1H), 7.97(d, *J* = 1.8Hz, 1H).
18 2-Cyclopropyl-6-hydroxymethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline
19 (Intermediate 24)

20 A stirred cooled (-78°C) solution of ethyl-2-cyclopropyl-4,4-dimethyl-
21 1,2,3,4-tetrahydro isoquinoline-6-carboxylate (Intermediate 23, 1g,
22 3.66mmol) in anhydrous dichloromethane (20mL) under argon was treated
23 with a 1M solution of di-*iso*-butyl aluminum hydride in dichloromethane
24 (10mL) and the reaction mixture was warmed to -20°C over 1h. It was then
25 quenched with saturated aqueous ammonium chloride solution and diluted
26 with dichloromethane and filtered over a bed of celite. The phases were
27 separated and the aqueous phase was extracted with dichloromethane (x1).
28 The combined organic extract was dried over anhydrous sodium sulfate,

1 filtered and evaporated in *vacuo* to afford the title compound as a viscous oil
2 (0.74g, 87%).

3 ¹H-NMR (300 MHz, CDCl₃): δ 0.45-0.53(m, 4H), 1.25(s, 6H), 1.72-1.82(m,
4 2H), 2.61(s, 2H), 3.73(s, 2H), 4.61 (d, *J* = 5Hz, 2H), 6.98(d, *J* = 7.9Hz, 1H),
5 7.07 (dd, *J* = 1.5, 7.6Hz, 1H), 7.27(s, 1H).

6 2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carbaldehyde
7 **(Intermediate 25)**

8 A solution of 2-cyclopropyl-6-hydroxymethyl-4,4-dimethyl-1,2,3,4-
9 tetrahydroisoquinoline (**Intermediate 24**, 0.74g, 3.2mmol) in dichloromethane
10 (10mL) and acetonitrile (2.5mL) was treated sequentially with 4A⁰ molecular
11 sieves powder (1.06g), tetra-*n*-propyl ammonium perruthenate (0.050g,
12 0.14mmol) and N-methyl morpholine N-oxide (1.1g, 9.8mmol). After stirring
13 at ambient temperature for 0.5h, it was diluted with 5mL of hexane and
14 subjected to flash column chromatography over silica gel (230-400 mesh)
15 using 10% ethyl acetate in hexane as the eluent to afford the title compound as
16 an oil (0.27g, 37%).

17 ¹H-NMR (300 MHz, CDCl₃):δ 0.44-0.56(m, 4H), 1.30(s, 6H), 1.79(m, 1H),
18 2.66(s, 2H), 3.82(s, 2H), 7.17(d, *J* = 7.9Hz, 1H), 7.60 (dd, *J* = 1.6, 7.9Hz, 1H),
19 7.82(d, *J* = 1.8Hz, 1H), 9.95 (s, 1H).

20 6-(2,2-Dibromo-vinyl)-2-cyclopropyl-4,4-dimethyl-1,2,3,4-
21 tetrahydroisoquinoline (**Intermediate 26**)

22 A stirred, cooled (ice-bath) solution of triphenyl phosphine (0.53g,
23 2mmol) in anhydrous dichloromethane was treated with carbon tetrabromide
24 (0.35g, 1mmol) under argon. After 0.5h, a solution of 2-cyclopropyl-4,4-
25 dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxaldehyde (**Intermediate 25**,
26 0.13g, 0.57mmol) in dichloromethane (2mL) was cannulated into the reaction
27 mixture. After 1.5h between 0°C and 10°C, the reaction mixture was subjected
28 to flash column chromatography over silica gel (230-400 mesh) using 3-5%

1 ethyl acetate in hexane as the eluent to afford the title compound as a viscous,
2 pale yellow oil (0.18g, 82%).
3 ¹H-NMR (300 MHz, CDCl₃): δ 0.49-0.57(m, 4H), 1.31(s, 6H), 1.80(m, 1H),
4 2.67(s, 2H), 3.77(s, 2H), 7.04(d, *J* = 7.9Hz, 1H), 7.29 (dd, *J* = 1.7, 7.9Hz, 1H),
5 7.49 (s, 1H), 7.50(d, *J* = 1.7Hz, 1H).

6 2-Cyclopropyl-6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline
7 **(Intermediate 27)**

8 A stirred, cooled (-78°C) solution of 6-(2,2-dibromo-vinyl)-2-
9 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxaldehyde
10 (**Intermediate 26**, 0.18g, 0.47mmol) in tetrahydrofuran (2mL) was treated
11 with 1.6M solution of *n*-butyl lithium (0.6mL, 0.96mmol) under argon. The
12 reaction mixture was allowed to warm to -20°C over 1.5h, quenched with
13 saturated aqueous ammonium chloride solution and extracted with diethyl
14 ether (x2). The combined organic phase was dried over anhydrous magnesium
15 sulfate, filtered and evaporated in *vacuo* to afford the title compound as an oil
16 (0.1g, 94%).

17 ¹H-NMR (300 MHz, CDCl₃): δ 0.47-0.55(m, 4H), 1.28(s, 6H), 1.77(m, 1H),
18 2.63(s, 2H), 3.05(s, 1H), 3.67(s, 2H), 6.98(d, *J* = 7.6Hz, 1H), 7.26 (dd, *J* =
19 1.5, 7.9Hz, 1H), 7.46(d, *J* = 1.5Hz, 1H).

20 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethynyl]-
21 2-fluoro-phenyl]-acetic acid ethyl ester (**Compound 21**, General Formula 3)

22 Following general procedure F and using 2-cyclopropyl-6-ethynyl-4,4-
23 dimethyl-1,2,3,4-tetrahydro-isoquinoline(**Intermediate 27**, 0.13g,
24 0.571mmol), 2-fluoro-4-iodo phenyl acetic acid ethyl ester (**Reagent C**, 0.16g,
25 0.52mmol), triethyl amine (0.8mL), anhydrous tetrahydrofuran (2mL),
26 copper(I)iodide (0.051g, 0.27mmol) and
27 dichlorobis(triphenylphosphine)palladium(II) (0.1g, 0.14mmol) followed by
28 flash column chromatography over silica gel (230-400 mesh) using 10% ethyl
29 acetate in hexane as the eluent, 0.1g of the title compound was obtained as an

1 oil. It was further purified by preparative normal phase HPLC on a partisil-10
2 silica column using 10% ethyl acetate in hexane as the mobile phase (0.055g,
3 24%).

4 ¹H-NMR (300 MHz, CDCl₃): δ 0.42-0.51(m, 4H), 1.26(t, *J* = 7.3Hz, 3H),
5 1.27(s, 6H), 1.75(m, 1H), 2.61(s, 2H), 3.66(s, 2H), 3.74(s, 2H), 4.18 (q, *J* =
6 7.3Hz, 2H), 6.97 (d, *J* = 7.9Hz, 1H), 7.20-7.29(m, 4H), 7.45(d, *J* = 1.5Hz,
7 1H).

8 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-
9 2-fluoro-phenyl]-acetic acid (Compound 22, General Formula 3)

10 Following general procedure J and using [4-(2-cyclopropyl-4,4-
11 dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-ylethynyl)-2-fluoro-phenyl]-acetic
12 acid ethyl ester (**Compound 21**, 0.055g, 0.135mmol), methanol (2mL),
13 tetrahydrofuran (4mL), water (1mL) and lithium hydroxide monohydrate
14 (0.117g, 2.97mmol) the title compound was obtained as a pale yellow solid
15 foam (0.040g, 78%).

16 ¹H-NMR (300 MHz, CDCl₃): δ 0.52-0.65(m, 4H), 1.27(s, 6H), 1.84(m, 1H),
17 2.71(s, 2H), 3.61(s, 2H), 3.85(s, 2H), 6.98(d, *J* = 7.9Hz, 1H), 7.06 (t, *J* =
18 7.6Hz, 1H), 7.17-7.25(m, 3H), 7.43(d, *J* = 1.2Hz, 1H), 8.60-9.00(br s, 1H).

19 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-
20 phenyl]-acetic acid methyl ester (Compound 23, General Formula 3)

21 Following general procedure F and using 2-cyclopropyl-4,4-dimethyl-
22 6-ethynyl-1,2,3,4-tetrahydro-isoquinoline(**Intermediate 27**, 0.13g,
23 0.571mmol), 4-iodo phenyl acetic acid methyl ester (**Reagent B**, 0.16g,
24 0.58mmol), triethyl amine (0.5mL), anhydrous tetrahydrofuran (2mL),
25 copper(I)iodide (0.04g, 0.21mmol) and
26 dichlorobis(triphenylphosphine)palladium(II) (0.12g, 0.17mmol) followed by
27 flash column chromatography over silica gel (230-400 mesh) using 10% ethyl
28 acetate in hexane as the eluent, 0.05g of the title compound was obtained as an
29 oil. It was further purified by preparative normal phase HPLC on a partisil-10

1 silica column using 10% ethyl acetate in hexane as the mobile phase (0.01g,
2 6%).
3 ¹H-NMR (300 MHz, CDCl₃): δ 0.42-0.58(m, 4H), 1.29(m, 6H), 1.79(m, 1H),
4 2.64(s, 2H), 3.67(s, 3H), 3.72(s, 2H), 3.77(s, 2H), 7.09 (d, *J* = 7.9Hz, 1H),
5 7.28(dd, *J* = 1.5, 7.9Hz, 1H), 7.36 (d, *J* = 7.9Hz, 2H), 7.50 (d, *J* = 1.6Hz, 1H),
6 7.51(d, *J* = 7.9Hz, 2H).

7 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-
8 phenyl]-acetic acid (Compound 24, General Formula 3)

9 Following general procedure J and using [4-(2-cyclopropyl-4,4-
10 dimethyl-1,2,3,4-tetrahydro-isoquinolin-6ylethynyl)-phenyl]-acetic acid
11 methyl ester (**Compound 23**, 0.01g, 0.027mmol), methanol (1mL),
12 tetrahydrofuran (1mL), water (0.5mL) and lithium hydroxide monohydrate
13 (0.042g, 1mmol) the title compound was obtained as a pale yellow solid foam
14 (0.0065g, 68%).

15 ¹H-NMR (300 MHz, CDCl₃): δ 0.35-0.52(m, 4H), 1.24(s, 6H), 1.74(m, 1H),
16 2.59(s, 2H), 3.64(s, 2H), 3.71(s, 2H), 7.03 (d, *J* = 8.2Hz, 1H), 7.22(dd, *J* =
17 1.4, 7.9Hz, 1H), 7.33 (d, *J* = 8.2Hz, 2H), 7.46 (d, *J* = 8.2Hz, 2H), 7.47(s, 1H).
18 1-(Iso-propyl-methyl-amino)-6-trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-
19 tetrahydro-naphthalene (Intermediate 28)

20 Following general procedure G and using a solution of 4,4-dimethyl-6-
21 trimethylsilanylethynyl-1,2,3,4-tetrahydro-naphthalene 2-one (**Intermediate**
22 **12**, 0.2g, 0.78mmol), dichloromethane (4mL), acetonitrile (2mL), acetic acid
23 (1mL), isopropyl amine (1mL, 11.74mmol) and sodium cyanoborohydride
24 (0.19g, 3.02mmol), after 15days of reaction time and work up afforded an
25 intermediate (0.14g, 60%, 0.47mmol) which was used following general
26 procedure H along with acetone (2mL), potassium carbonate (0.6g, 4.34mmol)
27 and methyl iodide (0.5mL, 8mmol). The crude product after work up was
28 subjected to flash column chromatography over silica gel (230-400 mesh)

1 using 15% ethyl acetate in hexane as the eluent to afford the title compound as
2 a pale yellow oil (0.14g, 95%).

3 ¹H-NMR (300 MHz, CDCl₃): δ 0.001(s, 9H), 0.85 (d, *J* = 6.4Hz, 6H), 0.98 (s,
4 3H), 1.03 (s, 3H), 1.32-1.60 (m, 4H), 1.81(s, 3H), 2.64(heptet, *J* = 6.4Hz, 1H),
5 3.65 (dd, *J* = 6.1, 9.4Hz, 1H), 6.97 (dd, *J* = 1.7, 7.9Hz, 1H), 7.13 (d, *J* =
6 1.7Hz, 1H), 7.82 (d, *J* = 7.9Hz, 1H).

7 6-Ethynyl-1-(*iso*-propyl-methyl-amino)-4,4-dimethyl-1,2,3,4-tetrahydro-
8 naphthalene (Intermediate 29)

9 Following general procedure E and using 1-(methyl-*iso*-propylamino)-
10 4,4-dimethyl-6-trimethylsilanylethynyl-1,2,3,4-tetrahydro-naphthalene
11 (Intermediate 28, 0.14g, 0.45mmol), methanol (5mL), potassium carbonate
12 (0.61g, 4.41mmol) and ethyl acetate the title compound (0.092g, 80%) was
13 obtained as an oil.

14 ¹H-NMR (300 MHz, CDCl₃): δ 1.11(d, *J* = 6.4Hz, 6H), 1.23(s, 3H), 1.28(s,
15 3H), 1.51-1.87 (m, 4H), 2.09(s, 3H), 2.90 (heptet, *J* = 6.4Hz, 1H), 3.00(s, 1H),
16 3.91 (dd, *J* = 5.8, 10.0Hz, 1H), 7.25(dd, *J* = 1.7, 8.2Hz, 1H), 7.41 (d, *J* =
17 1.7Hz, 1H), 7.70(d, *J* = 8.2Hz, 1H).

18 4-[5-(*Is*o-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-
19 2-yl-ethynyl]-benzoic acid ethyl ester (Compound 25, General Formula 4)

20 Following general procedure F and 6-ethynyl-1-(*iso*-propyl-methyl-
21 amino)-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalene (Intermediate 29,
22 0.092g, 0.36mmol), ethyl-4-iodo benzoate (Reagent A, 0.12g, 0.48mmol),
23 triethyl amine (1mL), tetrahydrofuran (2mL), copper(I)iodide (0.028g,
24 0.14mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.075g,
25 0.11mmol) followed by flash column chromatography over silica gel (230-400
26 mesh) using 10-15% ethyl acetate in hexane as the eluent the title compound
27 was obtained (0.04g, 27%).

28 ¹H-NMR (300 MHz, CDCl₃): δ 1.12 (d, *J* = 6.5Hz, 6H), 1.27 (s, 3H), 1.31 (s,
29 3H), 1.40 (t, *J* = 7.0Hz, 3H), 1.62-1.89 (m, 4H), 2.10(s, 3H), 2.92 (heptet, *J* =

1 6.4Hz, 1H), 3.94(dd, $J = 6.1, 9.7$ Hz, 1H), 4.38(q, $J = 7.1$ Hz, 2H), 7.31(dd, $J =$
2 1.4, 8.2Hz, 1H), 7.46 (d, $J = 1.7$ Hz, 1H), 7.58 (d, $J = 8.2$ Hz, 2H), 7.75(d, $J =$
3 8.2Hz, 1H), 8.01(d, $J = 8.2$ Hz, 2H).

4 4-[5-(*Iso*-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-
5 2-yl-ethynyl)]-benzoic acid (Compound 26, General Formula 4)

6 Following general procedure I and using 4-[5-(*iso*-propyl-methyl-
7 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)]-benzoic
8 acid ethyl ester (Compound 25, 0.04g, 0.01mmol), ethanol (2mL),
9 tetrahydrofuran (1mL) and 1M aqueous sodium hydroxide solution (1mL)
10 followed by recrystallization from diethylether-hexane, the title compound
11 was obtained as an off-white solid (0.010g, 27%).
12 ¹H-NMR (300 MHz, CDCl₃): δ 1.30(d, $J = 6.0$ Hz, 6H), 1.31(s, 9H), 1.67-
13 1.98(m, 4H), 2.35 (s, 3H), 3.19 (heptet, $J = 6.4$ Hz, 1H), 4.36 (t, $J = 7.6$ Hz,
14 1H), 7.28(dd, $J = 1.4, 8.2$ Hz, 1H), 7.48 (d, $J = 1.4$ Hz, 1H), 7.55 (d, $J = 8.2$ Hz,
15 2H), 7.81 (d, $J = 8.2$ Hz, 1H), 8.05 (d, $J = 8.2$ Hz, 2H).
16 [4-(2,2,4,4-Tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid methyl
17 ester (Compound 27, General Formula 8)

18 Following general procedure F and using 6-ethynyl-2,2,4,4-
19 tetramethylchroman (synthesis described in U.S. Patent Nos. 5,045,551 and
20 5,616,597 incorporated herein by reference) (0.060g, 0.28mmol), methyl-4-
21 iodo phenyl acetate (Reagent B, 0.078g, 0.28mmol), triethyl amine (4mL),
22 tetrahydrofuran (4mL), copper(I)iodide (0.030g, 0.16mmol) and
23 dichlorobis(triphenylphosphine)palladium(II) (0.11g, 0.16mmol) followed by
24 flash column chromatography over silica gel (230-400 mesh) using 5-10 %
25 ethyl acetate in hexane as the eluent the title compound was obtained (0.047g,
26 46%).
27 ¹H NMR (300 MHz, CDCl₃): δ 7.48-7.45 (m, 3H), 7.25-7.23 (m, 3H), 6.75 (d,
28 1H, $J = 8.2$ Hz), 3.70 (s, 3H), 3.62 (s, 2H), 1.84 (s, 2H), 1.36 (s, 6H), 1.35 (s,
29 6H).

1 GENERAL PROCEDURE L: [4-(2,2,4,4-Tetramethyl-chroman-6-yl-ethynyl)
2 phenyl] acetic acid (Compound 28, General Formula 8)

3 A solution of [4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl]
4 acetic acid methyl ester (Compound 27, 0.047g, 0.13mmol) in 5mL of
5 methanol was treated with 1M sodium hydroxide solution (2mL) and heated at
6 55°C for 2h. The volatiles were distilled off in *vacuo* and the residue was
7 acidified with 10% hydrochloric acid and extracted with ethyl acetate (x2).
8 The combined organic phase was washed with brine (x1), dried over
9 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue which
10 was purified by preparative reverse phase HPLC using 10% water in
11 acetonitrile as the mobile phase to afford the title compound (0.034g, 82%). ¹H
12 NMR (300 MHz, CDCl₃): δ 7.49-7.45 (m, 3H), 7.26-7.22 (m, 3H), 6.75 (d,
13 1H, *J* = 8.2Hz), 3.65 (s, 2H), 1.84 (s, 2H), 1.36 (s, 6H), 1.35 (s, 6H).

14 2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid methyl
15 ester (Compound 29, General Formula 8)

16 Following general procedure F and using 6-ethynyl-2,2,4,4-
17 tetramethylchroman (0.11g, 0.51mmol), methyl-2-fluoro-4-iodo-benzoate
18 (Reagent G, 0.14g, 0.51mmol), triethyl amine (5mL), tetrahydrofuran(10mL),
19 copper(I)iodide(0.030g, 0.16mmol) and
20 dichlorobis(triphenylphosphine)palladium(II) (0.110g, 0.16mmol) followed by
21 flash column chromatography over silica gel (230-400 mesh) using 5-10 %
22 ethyl acetate in hexane as the eluent, the title compound was obtained (0.14g,
23 79%).

24 ¹H NMR (300 MHz, CDCl₃): δ 7.82 (t, 1H, *J* = 7.9Hz), 7.39 (d, 1H, *J* =
25 1.8Hz), 7.25-7.16 (m, 3H), 6.69 (d, 1H, *J* = 8.2Hz), 3.85 (s, 3H), 1.77 (s, 2H),
26 1.29 (s, 6H), 1.28 (s, 6H).

27 2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid
28 (Compound 30, General Formula 8)

1 Following general procedure L and using 2-fluoro-4-(2,2,4,4-
2 tetramethyl-chroman-6-yl-ethynyl)-benzoic acid methyl ester (**Compound 29**,
3 0.14g, 0.4mmol), 5mL of methanol and 1M sodium hydroxide solution (2mL)
4 followed by recrystallization from ethyl acetate, the title compound was
5 obtained (0.083g, 58%).

6 ¹H NMR (300 MHz, CD₃COCD₃): δ 8.00 (t, 1H, *J* = 7.8Hz), 7.63 (d, 1H, *J* =
7 2.1Hz), 7.45 (dd, 1H, *J* = 1.5, 7.9Hz), 7.38 (dd, 1H, *J* = 1.5, 11.4Hz), 7.32 (dd,
8 1H, *J* = 2.1, 8.2Hz), 6.81 (d, 1H, *J* = 8.5Hz), 1.92 (s, 2H), 1.41 (s, 6H), 1.38 (s,
9 6H).

10 [2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid
11 ethyl ester (**Compound 31, General Formula 8**)

12 Following general procedure F and using 6-ethynyl-2,2,4,4-
13 tetramethylchroman (0.204g, 0.95mmol), ethyl-2-fluoro-4-iodo phenyl acetate
14 (**Reagent C**, 0.263g, 0.86mmol), triethyl amine, tetrahydrofuran,
15 copper(I)iodide (0.025g, 0.13mmol) and
16 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) followed by
17 flash column chromatography over silica gel (230-400 mesh) using 5-10 %
18 ethyl acetate in hexane as the eluent, the title compound was obtained (0.21g,
19 62%).

20 ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, 1H, *J* = 2.1Hz), 7.25-7.21 (m, 4H),
21 6.69 (d, 1H, *J* = 8.5Hz), 4.16 (q, 2H, *J* = 7.1Hz), 3.65 (s, 2H), 1.82 (s, 2H),
22 1.35 (s, 6H), 1.35 (s, 6H), 1.24 (t, 3H, *J* = 7.2Hz).

23 [2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid
24 (**Compound 32, General Formula 8**)

25 Following general procedure L and using [2-fluoro-4-(2,2,4,4-
26 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid ethyl ester (**Compound**
27 **31**, 0.21g, 0.58mmol), 5mL of methanol and 1M sodium hydroxide solution
28 (2mL) followed by flash column chromatography over silica gel (230-400

1 mesh) using 50% ethyl acetate in hexane, the title compound was obtained as a
2 solid (0.184g, 93%).

3 ¹H NMR (300 MHz, CDCl₃): δ 11.40 (br s, 1H), 7.48 (d, 1H, *J* = 1.8Hz), 7.46-
4 7.16 (m, 4H), 6.76 (d, 1H, *J* = 8.2Hz), 3.69 (s, 2H), 1.82 (s, 2H), 1.34 (s, 12H).

5 3-Methyl-but-2-enoic acid 4-bromo-phenyl ester:

6 To a stirred, cooled (ice bath) suspension of sodium hydride (2.4g,
7 100mmol) in anhydrous tetrahydrofuran (200mL), 4-bromo phenol (17.3g,
8 100mmol) was added followed by 3,3,-dimethyl acryloyl chloride (11.14mL,
9 100mmol). After 4hours at ambient temperature, the reaction mixture was
10 poured into brine and extracted with diethyl ether (x2). The combined organic
11 phase was dried over anhydrous sodium sulfate, filtered and evaporated in
12 *vacuo* to afford an oil which was subjected to flash column chromatography
13 over silica gel (230-400 mesh) using 2% ethyl acetate in hexane as the eluent
14 to afford the title compound (15g, 59%).

15 ¹H-NMR (300 MHz, CDCl₃):δ 2.00(s, 3H), 2.23(s, 3H), 5.89(s, 1H), 7.00(d, *J*
16 = 8.8Hz, 2H), 7.49(d, *J* = 8.8Hz, 2H).

17 6-Bromo-4,4-dimethyl-chroman-2-one:

18 A solution of 3-methyl-but-2-enoic acid 4-bromo-phenyl ester (7g,
19 27.6mmol) in anhydrous dichloromethane (200mL) was cooled (ice bath) and
20 treated with aluminum chloride (6.6g, 49.6mmol) and the reaction mixture was
21 stirred overnight at ambient temperature. The reaction mixture was quenched
22 with saturated aqueous sodium bicarbonate solution and extracted with diethyl
23 ether (x2). The combined organic extract was washed with brine (x1), dried
24 over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford an
25 oil which was purified by flash column chromatography over silica gel (230-
26 400 mesh) using 2.5% ethyl acetate in hexane as the eluent to afford the title
27 compound (4.2g, 57%).

28 ¹H-NMR (300 MHz, CDCl₃):δ 1.36(s, 6H), 2.62(s, 2H), 6.95(d, *J* = 8.5Hz,
29 1H), 7.37(dd, *J* = 2.4, 8.5Hz, 1H), 7.43(d, *J* = 2.3Hz, 1H).

1 4-Bromo-2-(3-hydroxy-1,1,3-trimethyl-butyl)-phenol:

2 A solution of 6-bromo-4,4-dimethyl-chroman-2-one (1g, 3.92mmol) in
3 anhydrous tetrahydrofuran (20mL) was treated with 3M solution of ethyl
4 magnesium bromide (2.6mL) and stirred at ambient temperature for 2hours.
5 The reaction mixture was poured into cold dilute hydrochloric acid and
6 extracted with ethyl acetate (x2). The combined organic extract was dried
7 over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford a
8 residue which was subjected to flash column chromatography over silica gel
9 (230-400 mesh) using 10% ethyl acetate in hexane as the eluent to afford the
10 title compound as a pale yellow solid (1.1g, 100%).

11 ¹H-NMR (300 MHz, CDCl₃):δ 1.14(s, 6H), 1.44(s, 6H), 2.20(s, 2H), 6.49(d, *J*
12 = 8.4Hz, 1H), 7.15(dd, *J* = 2.4, 8.5Hz, 1H), 7.37(d, *J* = 2.4Hz, 1H).

13 6-Bromo-2,2,4,4-tetramethyl-chroman:

14 A solution of 4-bromo-2-(3-hydroxy-1,1,3-trimethyl-butyl)-phenol
15 (1.1g, 3.92mmol) and *p*-toluene sulfonic acid (0.744g, 3.92mmol) in benzene
16 (20mL) was refluxed overnight. The reaction mixture cooled to ambient
17 temperature, filtered on silica gel and washed with 10% ethyl acetate in
18 hexane. The filtrate and washings were evaporated in *vacuo* to an oil which
19 was subjected to flash column chromatography over silica gel (230-400 mesh)
20 using 5% ethyl acetate in hexane as the eluent to afford the title compound as a
21 pale yellow oil (0.84g, 80%).

22 ¹H-NMR (300 MHz, CDCl₃):δ 1.34(s, 6H), 1.35(s, 6H), 1.82(s, 2H), 6.68(d, *J*
23 = 8.4Hz, 1H), 7.16(dd, *J* = 2.7, 8.7Hz, 1H), 7.37(d, *J* = 2.6Hz, 1H).

24 The synthesis of this compound, as described here, is in close analogy
25 to the synthesis of 6-bromo-2,2,4,4-tetramethylthiochroman, as described in
26 United States Patent No. 5,045,551

27 2,2,4,4-tetramethyl-6-(2-trimethylsilyl)ethynyl chroman:

28 Following general procedure D and using 6-bromo-2,2,4,4-tetramethyl
29 chroman (0.5g, 1.87mmol), triethyl amine (5mL), anhydrous tetrahydrofuran

1 (15mL), copper(I)iodide (0.107g, 0.156mmol), trimethylsilyl acetylene (1.84g,
2 18.7mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.39g,
3 0.56mmol) the title compound was obtained as a brown oil (0.61g, 100%).
4 ¹H NMR (300 MHz, CDCl₃): δ 7.43 (d, 1H, *J* = 2.1Hz), 7.23 (dd, 1H, *J* = 7.9,
5 2.1Hz), 6.73 (d, 1H, *J* = 8.2Hz), 1.83 (s, 2H), 1.36 (s, 12H), 0.28 (s, 9H).

6 6-Ethynyl-2,2,4,4-tetramethyl chroman:

7 Following general procedure E and using 2,2,4,4-tetramethyl-6-(2-
8 trimethylsilyl)ethynyl chroman (0.61g, 1.87mmol), potassium carbonate (1.9g,
9 13.74mmol) and methanol the title compound was obtained (0.4g, 90%).
10 ¹H NMR (300 MHz, CDCl₃): δ 7.47 (d, 1H, *J* = 2.1Hz), 7.24 (dd, 1H, *J* = 7.9,
11 2.1Hz), 6.76 (d, 1H, *J* = 8.2Hz), 3.01 (s, 1H), 1.85 (s, 2H), 1.37 (s, 6H), 1.36
12 (s, 6H).

13 An alternative synthesis for this compound is described in United States
14 Patent Nos. 5,045,551 and 5,616,597

15 GENERAL PROCEDURE M: 6-Bromo-2,2,4,4-tetramethyl-chroman-8-
16 carbaldehyde (Intermediate 30)

17 A stirred, cooled (ice bath) solution of 6-bromo-2,2,4,4-tetramethyl
18 chroman, (0.5g, 1.865mmol) in anhydrous dichloromethane (5mL) was treated
19 with a 1M solution (1.86mL, 1.86mmol) of titanium tetrachloride in
20 dichloromethane followed by α,α-dichloro methyl ether (0.214g, 1.865mmol).
21 The reaction mixture was allowed to warm to ambient temperature for 4h. The
22 reaction mixture was diluted with diethyl ether, washed with brine (x1) and
23 dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a
24 residue which was subjected to flash column chromatography over silica gel
25 (230-400 mesh) using 5% ethyl acetate in hexane to afford the title compound
26 as a yellow solid (0.52g, 94%).
27 ¹H NMR (300 MHz, CDCl₃): δ 10.38 (s, 1H), 7.72 (d, 1H, *J* = 2.6Hz), 7.57 (d,
28 1H, *J* = 2.6Hz), 1.88 (s, 2H), 1.41 (s, 6H), 1.36 (s, 6H).

1 GENERAL PROCEDURE N: 6-Bromo-8-vinyl-2,2,4,4-tetramethyl-chroman
2 (**Intermediate 31**)

3 A solution of methylenetriphenyl phosphorane [generated from
4 methyltriphenylphosphonium bromide (7g, 20mmol) and (11.8mL, 19mmol)
5 of a 1.6M solution of *n*-butyllithium in hexanes] was added 6-bromo-2,2,4,4-
6 tetramethyl chroman-8-carbaldehyde (**Intermediate 30**, 0.52g, 1.75mmol).
7 After 1h the reaction mixture was diluted with hexane, washed with brine (x1),
8 dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a
9 clear oil which was subjected to flash column chromatography over silica gel
10 (230-400 mesh) using 2% ethyl acetate in hexane as the eluent to afford the
11 title compound as a clear oil (0.37g, 72%).

12 ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, 1H, *J* = 2.5Hz), 7.33 (d, 1H, *J* =
13 2.5Hz), 7.03 (dd, 1H, *J* = 11.3, 17.9Hz), 5.75 (dd, 1H, *J* = 1.4, 17.9Hz), 5.30
14 (dd, 1H, *J* = 1.4, 11.3Hz), 1.85 (s, 2H), 1.39 (s, 6H), 1.37 (s, 6H).

15 GENERAL PROCEDURE O: 6-Bromo-8-cyclopropyl-2,2,4,4-tetramethyl
16 chroman (**Intermediate 32**)

17 A stirred, cooled (-30°C) solution of 6-bromo-8-vinyl-2,2,4,4-
18 tetramethyl chroman (**Intermediate 31**, 0.37g, 1.26mmol) in diethyl ether was
19 treated with a solution of diazomethane in diethyl ether and catalytic amount
20 of palladium (II)acetate (~30mg). The reaction mixture was allowed to warm
21 to ambient temperature and subjected to flash column chromatography over
22 silica gel (230-400 mesh) using 2% ethyl acetate in hexane as the eluent to
23 afford the title compound as a clear, pale yellow oil (0.376g, 97%).

24 ¹H NMR (300 MHz, CDCl₃): δ 7.17 (d, 1H, *J* = 2.3Hz), 6.73 (d, 1H, *J* =
25 2.6Hz), 2.19-2.16 (m, 1H), 1.83 (s, 2H), 1.37 (s, 6H), 1.33 (s, 6H), 0.94-0.88
26 (m, 2H), 0.64-0.59 (m, 2H).

27 8-Cyclopropyl-6-trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman
28 (**Intermediate 33**)

1 Following general procedure D and using 6-bromo-8-cyclopropyl-
2 2,2,4,4-tetramethyl chroman (**Intermediate 32**, 0.376g, 1.22mmol),
3 (trimethylsilyl)acetylene (4mL, 28mmol), triethyl amine (3mL), anhydrous
4 tetrahydrofuran (5mL), copper(I)iodide (0.025g, 0.13mmol) and
5 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), the title
6 compound was obtained as an oil (0.173g, 43%).
7 ¹H NMR (300 MHz, CDCl₃): δ 7.36 (d, 1H, *J* = 2.2Hz), 6.90 (d, 1H, *J* =
8 1.9Hz), 2.31-2.22 (m, 1H), 1.96 (s, 2H), 1.49 (s, 6H), 1.46 (s, 6H), 1.05-0.88
9 (m, 2H), 0.78-0.72 (m, 2H), 0.37 (s, 9H).

10 8-Cyclopropyl-6-ethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 34**)

11 Following general procedure E and using 8-cyclopropyl-6-
12 trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 33**, 0.17g,
13 0.68mmol), methanol and potassium carbonate (0.2g, 1.47mmol) the title
14 compound was obtained as an oil (0.064g, 47%).
15 ¹H NMR (300 MHz, CDCl₃): δ 7.38 (d, 1H, *J* = 1.9Hz), 6.92 (d, 1H, *J* =
16 1.9Hz), 3.08 (s, 1H), 2.32-2.23 (m, 1H), 1.96 (s, 2H), 1.50 (s, 6H), 1.46 (s,
17 6H), 1.05-0.99 (m, 2H), 0.77-0.72 (m, 2H).

18 4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid
19 ethyl ester (**Compound 33**, General Formula 8)

20 Following general procedure F and using 8-cyclopropyl-6-ethynyl-
21 2,2,4,4-tetramethylchroman (**Intermediate 34**, 0.1g, 0.38mmol), ethyl-4-iodo-
22 benzoate (**Reagent A**, 0.1g, 0.34mmol), triethyl amine (5mL),
23 tetrahydrofuran(10mL), copper(I)iodide(0.025g, 0.13mmol) and
24 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) followed by
25 flash column chromatography over silica gel (230-400 mesh) using 5-10 %
26 ethyl acetate in hexane as the eluent, the title compound was obtained (0.135g,
27 89%).
28 ¹H NMR (300 MHz, CDCl₃): δ 8.00 (d, 2H, *J* = 8.2Hz), 7.55 (d, 2H, *J* =
29 8.2Hz), 7.30 (d, 1H, *J* = 1.8Hz), 6.84 (d, 1H, *J* = 2.0Hz), 4.38 (q, 2H, *J* =

1 6.9Hz), 2.22-2.12 (m, 1H), 1.85 (s, 2H), 1.40 (t, 3H, $J = 6.9\text{Hz}$), 1.38 (s, 6H),
2 1.36 (s, 6H), 0.92-0.88 (m, 2H), 0.67-0.62 (m, 2H).

3 4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid
4 **(Compound 34, General Formula 8)**

5 Following general procedure L and using 4-(8-cyclopropyl-2,2,4,4-
6 tetramethyl-chroman-6-yl-ethynyl)-benzoic acid ethyl ester (**Compound 33**,
7 0.135g, 0.34mmol), 5mL of methanol and 1M sodium hydroxide solution
8 (2mL) followed by preparative reverse phase HPLC using 10% water in
9 acetonitrile as the mobile phase, the title compound was obtained as a solid
10 (0.093g, 73%).

11 ^1H NMR (300 MHz, CDCl_3): δ 11.26 (br s, 1H), 8.08 (d, 2H, $J = 8.2\text{Hz}$), 7.59
12 (d, 2H, $J = 8.2\text{Hz}$), 7.31 (d, 1H, $J = 1.8\text{Hz}$), 6.85 (d, 1H, $J = 2.1\text{Hz}$), 2.22-2.13
13 (m, 1H), 1.85 (s, 2H), 1.38 (s, 6H), 1.36 (s, 6H), 0.95-0.87 (m, 2H), 0.68-0.63
14 (m, 2H).

15 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic
16 acid methyl ester (**Compound 35, General Formula 8**)

17 Following general procedure F and using 8-cyclopropyl-6-ethynyl-
18 2,2,4,4-tetramethylchroman (**Intermediate 34**, 0.096g, 0.38mmol), methyl-4-
19 iodo phenyl acetate (**Reagent B**, 0.094g, 0.34mmol), triethyl amine (3mL),
20 tetrahydrofuran (3mL), copper(I)iodide (0.025g, 0.13mmol) and
21 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) the title
22 compound was obtained (0.137g, 90%). ^1H NMR (300 MHz, CDCl_3): δ 7.47
23 (d, 2H, $J = 7.9\text{Hz}$), 7.29 (d, 1H, $J = 1.8\text{Hz}$), 7.24 (d, 2H, $J = 7.9\text{Hz}$), 6.82 (d,
24 1H, $J = 2.1\text{Hz}$), 3.70 (s, 3H), 3.63 (s, 2H), 2.22-2.13 (m, 1H), 1.85 (s, 2H),
25 1.38 (s, 6H), 1.36 (s, 6H), 0.94-0.86 (m, 2H), 0.68-0.63 (m, 2H).

26 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic
27 acid (**Compound 36, General Formula 8**)

28 Following general procedure L and using [4-(8-cyclopropyl-2,2,4,4-
29 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid methyl ester

1 (Compound 35, 0.137g, 0.30mmol), 5mL of methanol and 1M sodium
2 hydroxide solution (2mL) followed by preparative reverse phase HPLC using
3 10% water in acetonitrile as the mobile phase, the title compound was
4 obtained as a solid (0.11g, 80%).
5 ¹H NMR (300 MHz, CDCl₃): δ 11.56 (br s, 1H), 7.47 (d, 2H, *J* = 8.9Hz), 7.28
6 (d, 1H, *J* = 1.9Hz), 7.23 (d, 2H, *J* = 8.5Hz), 6.82 (d, 1H, *J* = 1.9Hz), 3.62 (s,
7 2H), 2.21-2.12 (m, 1H), 1.83 (s, 2H), 1.36 (s, 6H), 1.34 (s, 6H), 0.93-0.82 (m,
8 2H), 0.72-0.62 (m, 2H).

9 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl]
10 acetic acid ethyl ester (Compound 37, General Formula 8)

11 Following general procedure F and using 8-cyclopropyl-6-ethynyl-
12 2,2,4,4-tetramethylchroman (Intermediate 34, 0.096g, 0.38mmol), ethyl-2-
13 fluoro-4-iodo phenyl acetate (Reagent C, 0.104g, 0.34mmol), triethyl amine
14 (3mL), tetrahydrofuran (3mL), copper(I)iodide (0.020g, 0.1mmol) and
15 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) the title
16 compound was obtained (0.14g, 85%).
17 ¹H NMR (300 MHz, CDCl₃): δ 7.31 (d, 1H, *J* = 1.9Hz), 7.29-7.21 (m, 3H),
18 6.85 (d, 1H, *J* = 1.9Hz), 4.20 (q, 2H, *J* = 7.1Hz), 3.68 (s, 2H), 2.24-2.14 (m,
19 1H), 1.87 (s, 2H), 1.40 (s, 6H), 1.38 (s, 6H), 1.28 (t, 3H, *J* = 7.1Hz), 0.96-0.85
20 (m, 2H), 0.70-0.64 (m, 2H).

21 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl]
22 acetic acid (Compound 38, General Formula 8)

23 Following general procedure L and using [4-(8-cyclopropyl-2,2,4,4-
24 tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl] acetic acid ethyl ester
25 (Compound 37, 0.14g, 0.323mmol), 5mL of methanol and 1M sodium
26 hydroxide solution (2mL) followed by reverse phase HPLC using 10% water
27 in acetonitrile as the mobile phase, the title compound was obtained as a solid
28 (0.110g, 80%).

1 ¹H NMR (300 MHz, CDCl₃): δ 7.28 (d, 1H, *J* = 2.1Hz), 7.27-7.17 (m, 3H),
2 6.82 (d, 1H, *J* = 1.8Hz), 3.70 (s, 2H), 2.21-2.11 (m, 1H), 1.84 (s, 2H), 1.37 (s,
3 6H), 1.35 (s, 6H), 0.94-0.87 (m, 2H), 0.67-0.62 (m, 2H).

4 GENERAL PROCEDURE P: 6-Bromo-4,4-dimethyl-2-methylene chroman
5 (**Intermediate 35**)

6 A stirred, cooled (ice bath) solution of 6-bromo-4,4-dimethyl-chroman-
7 2-one available in accordance with U.S. Patent No. 5,399,561 incorporated
8 herein by reference (1g, 3.92mmol) in 8mL of anhydrous tetrahydrofuran was
9 treated with a 0.5 M solution of μ-chloro-μ-methylene-
10 [bis(cyclopentadienyl)titanium]dimethylaluminum (Tebbe reagent) in toluene
11 (8.23mL, 4.12mmol). After 10 minutes, the reaction mixture was poured into
12 ice-water mixture containing 50mL of 1M sodium hydroxide and extracted
13 with hexane. The hexane extract was washed with brine (x1), filtered over a
14 bed of celite and evaporated in *vacuo* to an oil which was subjected to flash
15 column chromatography over silica gel (230-400 mesh) using hexane as the
16 eluent to afford the title compound (0.74g, 74%) as a clear oil.

17 ¹H NMR (300 MHz, CDCl₃): δ 7.34 (d, 1H, *J* = 2.3Hz), 7.23 (dd, 1H, *J* =
18 2.3, 8.5Hz), 6.77 (d, 1H, *J* = 8.0Hz), 4.61 (d, 1H, *J* = 0.73Hz), 4.17 (d, 1H, *J* =
19 0.73Hz), 2.33 (s, 2H), 1.27 (s, 6H).

20 GENERAL PROCEDURE Q: 6-Bromo-3,4-dihydro-4,4-dimethylspiro[2H-1-
21 benzopyran-2,1'-cyclopropane] (**Intermediate 36**)

22 A solution of diethyl zinc in hexane (1M, 7.1mL) was treated with
23 diiodomethane (1.89g, 7.1mmol). After 5 minutes, a solution of 6-bromo-4,4-
24 dimethyl-2-methylene chroman (**Intermediate 35**, 0.44g, 1.77mmol) in 3mL
25 of hexane was added and the solution was refluxed for 1h. The reaction
26 mixture was then cooled to ambient temperature, diluted with hexane, washed
27 with brine (x1), dried over anhydrous sodium sulfate, filtered and evaporated
28 in *vacuo* to a residue which was subjected to flash column chromatography

1 over silica gel (230-400 mesh) using hexane as the eluent to obtain the title
2 compound (0.44g, 93%).

3 ¹H NMR (300 MHz, CDCl₃): δ 7.47 (d, 1H, *J* = 2.3Hz), 7.23 (dd, 1H, *J* =
4 2.3, 8.5Hz), 6.70 (d, 1H, *J* = 8.0Hz), 1.96 (s, 2H), 1.47 (s, 6H), 1.09-1.05 (m,
5 2H), 0.74-0.70 (m, 2H).

6 3,4-Dihydro-4,4-dimethyl-6-(trimethylsilanyl)ethynylspiro[2H-1-benzopyran-
7 2,1'-cyclopropane] (**Intermediate 37**)

8 Following general procedure D and using 6-bromo-3,4-dihydro-4,4-
9 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 36**, 0.44g,
10 1.65mmol), triethyl amine (4mL), anhydrous tetrahydrofuran (5mL),
11 copper(I)iodide (0.95g, 0.5mmol), trimethylsilyl acetylene (1.62g, 16.5mmol)
12 and dichlorobis(triphenylphosphine)palladium(II) (0.4g, 0.56mmol), the title
13 compound was obtained as a brown oil (0.4g, 86%).

14 ¹H NMR (300 MHz, CDCl₃): δ 7.44 (d, 1H, *J* = 2.1Hz), 7.18 (dd, 1H, *J* =
15 2.1, 8.5Hz), 6.65 (d, 1H, *J* = 8.5Hz), 1.87 (s, 2H), 1.37 (s, 6H), 1.01-0.97 (m,
16 2H), 0.65-0.61 (m, 2H), 0.26 (s, 9H).

17 6-Ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-
18 cyclopropane] (**Intermediate 38**)

19 Following general procedure E and using 3,4-dihydro-4,4-dimethyl-6-
20 (trimethylsilanyl)ethynylspiro[2H-1-benzopyran-2,1'-cyclopropane]
21 (**Intermediate 37**, 0.4g, 1.42mmol), potassium carbonate (0.98g, 7.1mmol)
22 and methanol, the title compound was obtained as a yellow oil (0.3g, 100%).

23 ¹H NMR (300 MHz, CDCl₃): δ 7.44 (d, 1H, *J* = 2.1Hz), 7.18 (dd, 1H, *J* = 2.1,
24 8.5Hz), 6.65 (d, 1H, *J* = 8.5Hz), 2.97 (s, 1H), 1.86 (s, 2H), 1.37 (s, 6H), 1.00-
25 0.95 (m, 2H), 0.64-0.59 (m, 2H).

26 Benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-
27 cyclopropane]-6-yl)ethynyl]-ethyl ester (**Compound 39, General Formula 1**)

28 Following general procedure F and using 6-ethynyl-3,4-dihydro-4,4-
29 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**, 0.06g,

1 0.28mmol), ethyl-4-iodo-benzoate (**Reagent A**, 0.086g, 0.31mmol), triethyl
2 amine (4mL), tetrahydrofuran(4mL), copper(I)iodide(0.032g, 0.17mmol) and
3 dichlorobis(triphenylphosphine)palladium(II) (0.118g, 0.17mmol) followed by
4 flash column chromatography over silica gel (230-400 mesh) using 5-10 %
5 ethyl acetate in hexane as the eluent, the title compound was obtained (0.07g,
6 70%).

7 ¹H NMR (300 MHz, CDCl₃): δ 8.01 (d, 2H, *J* = 8.2Hz), 7.56 (d, 2H, *J* =
8 8.5Hz), 7.49 (d, 1H, *J* = 2.1Hz), 7.24 (dd, 1H, *J* = 2.1, 8.5Hz), 6.70 (d, 1H, *J* =
9 8.5Hz), 4.38 (q, 2H, *J* = 7.1Hz), 1.89 (s, 2H), 1.40 (s, 6H), 1.40 (t, 3H, *J* =
10 7.0Hz), 1.02-0.98 (m, 2H), 0.67-0.62 (m, 2H).

11 Benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
12 cyclopropane]-6-yl)ethynyl]- (**Compound 40, General Formula 1**)

13 Following general procedure L and using benzoic acid, 4-[(3,4-dihydro-4,4-
14 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester
15 (**Compound 39**, 0.07g, 0.196mmol), 5mL of ethanol and 1M sodium
16 hydroxide solution (2mL) followed by preparative reverse phase HPLC using
17 10% water in acetonitrile as the mobile phase, the title compound was
18 obtained as a solid (0.034g, 52%).

19 ¹H NMR (300 MHz, CD₃COCD₃): δ 8.05 (d, 2H, *J* = 8.2Hz), 7.64 (d, 2H, *J* =
20 8.2Hz), 7.60 (d, 1H, *J* = 2.1Hz), 7.28 (dd, 1H, *J* = 2.1, 8.5Hz), 6.73 (d, 1H, *J* =
21 8.5Hz), 1.95 (s, 2H), 1.43 (s, 6H), 0.96-0.92 (m, 2H), 0.74-0.71 (m, 2H).

22 Benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
23 cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 41, General Formula**
24 **1**)

25 Following general procedure F and using 6-ethynyl-3,4-dihydro-4,4-
26 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**, ,
27 0.060g, 0.28mmol), methyl-4-iodo phenyl acetate (**Reagent B**, 0.078g,
28 0.28mmol), triethyl amine (4mL), tetrahydrofuran (4mL), copper(I)iodide
29 (0.032g, 0.17mmol) and dichlorobis(triphenylphosphine)palladium(II)

(0.118g, 0.17mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 5 % ethyl acetate in hexane as the eluent, the title compound was obtained (0.084g, 84%).

¹H NMR (300 MHz, CDCl₃): δ 7.48-7.45 (m, 3H), 7.26-7.20 (m, 3H), 6.67 (d, 1H, *J* = 8.5Hz), 3.70 (s, 3H), 3.63 (s, 2H), 1.89 (s, 2H), 1.40 (s, 3H), 1.40 (s, 3H), 1.01-0.97 (m, 2H), 0.67-0.61 (m, 2H).

Benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 42, Formula 1)

A solution of benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (Compound 41, 0.084g, 0.24mmol) in 5mL of methanol was treated with 1M sodium hydroxide solution (2mL) and heated at 55°C for 2h. The volatiles were distilled off in *vacuo* and the residue was acidified with 10% hydrochloric acid and extracted with ethyl acetate (x2). The combined organic phase was washed with brine (x1), dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue which was purified by preparative reverse phase HPLC using 10% water in acetonitrile as the mobile phase to afford the title compound (0.080g, 100%).

¹H NMR (300 MHz, CD₃COCD₃): δ 7.49-7.46 (m, 3H), 7.25 (d, 2H, *J* = 8.2Hz), 7.22 (dd, 1H *J* = 2.1, 8.5Hz), 6.68 (d, 1H, *J* = 8.5Hz), 3.66 (s, 2H), 1.88 (s, 2H), 1.44 (s, 6H), 1.01-0.97 (m, 2H), 0.67-0.61 (m, 2H).

2-Fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (Compound 43, General Formula 1)

Following general procedure F and 6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (Intermediate 38, 0.050g, 0.23mmol), methyl-2-fluoro-4-iodo-benzoate (Reagent G, 0.069g, 0.24mmol), triethyl amine (5mL), tetrahydrofuran(5mL), copper(I)iodide(0.013g, 0.07mmol) and

1 dichlorobis(triphenylphosphine)palladium(II) (0.049g, 0.07mmol) followed by
2 flash column chromatography over silica gel (230-400 mesh) using 5-10 %
3 ethyl acetate in hexane as the eluent, the title compound was obtained (0.080g,
4 100%).

5 ¹H NMR (300 MHz, CDCl₃): δ 7.90 (t, 1H, *J* = 7.9Hz), 7.63 (d, 1H, *J* =
6 1.8Hz), 7.32 (dd, 1H, *J* = 1.5, 8.2Hz), 7.26 (dd, 1H, *J* = 1.5, 11.4Hz), 7.24 (dd,
7 1H, *J* = 2.1, 8.5Hz), 6.71 (d, 1H, *J* = 8.5Hz), 1.97 (s, 2H), 1.44 (s, 6H), 0.98-
8 0.94 (m, 2H), 0.76-0.71 (m, 2H).

9 2-Fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-
10 2,1'-cyclopropane]-6-yl)ethynyl]- (**Compound 44, General Formula 1**)

11 Following general procedure L and using 2-fluoro-benzoic acid, 4-
12 [(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-
13 yl)ethynyl]-methyl ester (**Compound 43**, 0.08g, 0.23mmol), 5mL of methanol
14 and 2M sodium hydroxide solution (1mL) followed by flash column
15 chromatography over silica gel (230-400 mesh) using ethyl acetate as the
16 eluent, the title compound was obtained (0.020g, 25%).

17 ¹H NMR (300 MHz, CD₃COCD₃): δ 7.99 (t, 1H, *J* = 7.9Hz), 7.63 (d, 1H, *J* =
18 2.1Hz), 7.44 (dd, 1H, *J* = 1.5, 7.9Hz), 7.37 (dd, 1H, *J* = 1.5, 11.4Hz), 7.31 (dd,
19 1H, *J* = 2.1, 8.5Hz), 6.75 (d, 1H, *J* = 8.2Hz), 1.97 (s, 2H), 1.44 (s, 6H), 0.98-
20 0.94 (m, 2H), 0.76-0.71 (m, 2H).

21 GENERAL PROCEDURE R: 2,2,4,4-Tetramethyl-chroman-6-carboxylic acid
22 (**Intermediate 39**)

23 A stirred, cooled (-78°C) solution of 6-bromo-2,2,4,4-tetramethyl
24 chroman (1.2g, 4.47mmol) in 15mL of anhydrous tetrahydrofuran was treated
25 with a 1.7M solution of *tert*-butyl lithium solution in pentane (5.27mL,
26 8.9mmol). After 10 minutes at -78°C, carbon dioxide (generated from dry ice)
27 was bubbled into the reaction mixture. The reaction mixture was allowed to
28 warm to ambient temperature. The reaction mixture was diluted with ethyl
29 acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and

1 evaporated in *vacuo* to a residue which was subjected to flash column
2 chromatography over silica gel (230-400 mesh) using ethyl acetate as the
3 eluent to afford the title compound as a white solid (1.1g, 92%).
4 ¹H NMR (300 MHz, CDCl₃): δ 12.17 (br s, 1H), 8.09 (d, 1H, *J* = 2.1Hz), 7.85
5 (dd, 1H, *J* = 2.1, 8.5Hz), 6.83 (d, 1H, *J* = 8.2Hz), 1.87 (s, 2H), 1.39 (s, 6H),
6 1.37 (s, 6H).

7 2,2,4,4-Tetramethyl-chroman-6-carboxylic acid 4-(tert-
8 butoxycarbonylmethyl)phenyl ester (Compound 45, General Formula 8)

9 A solution of 2,2,4,4-tetramethyl chroman-6-carboxylic acid (0.1g,
10 0.43mmol) in thionyl chloride (10mL) was refluxed for 2h. The thionyl
11 chloride was evaporated under reduced pressure and the residue was dissolved
12 in 5mL of dichloromethane and treated with triethyl amine (5mL) followed by
13 *tert*-butyl-4-hydroxy phenyl acetate (Reagent E, 0.088g, 0.427mmol). After
14 0.5h, the reaction mixture was subjected to flash column chromatography over
15 silica gel (230-400 mesh) using 5-10% ethyl acetate in hexane as the eluent to
16 afford the title compound (0.1g, 55%).

17 ¹H NMR (300 MHz, CDCl₃): δ 8.15 (d, 1H, *J* = 2.1Hz), 7.93 (dd, 1H, *J* = 2.1,
18 8.5Hz), 7.33 (d, 2H, *J* = 8.8Hz), 7.16 (d, 2H, *J* = 8.8Hz), 6.88 (d, 1H, *J* =
19 8.5Hz), 3.54 (s, 2H), 1.89 (s, 2H), 1.45 (s, 9H), 1.41 (s, 6H), 1.40 (s, 6H).

20 2,2,4,4-Tetramethyl-chroman-6-carboxylic acid 4-(carboxymethyl)phenyl
21 ester (Compound 46, General Formula 8)

22 A solution of 2,2,4,4-tetramethyl-chroman-6-carboxylic acid 4-(*tert*-
23 butoxycarbonylmethyl)phenyl ester (Compound 45, 0.1g, 0.23mmol) was
24 treated with 5mL of trifluoroacetic acid and stirred at ambient temperature for
25 1h. The trifluoroacetic acid was distilled off under reduced pressure and the
26 residue was subjected to preparative reverse phase HPLC using 10% water in
27 acetonitrile as the mobile phase to afford the title compound as a white solid
28 (0.045g, 50%).

¹H NMR (300 MHz, CDCl₃): δ 8.13 (d, 1H, *J* = 2.1Hz), 7.92 (dd, 1H, *J* = 2.3, 8.5Hz), 7.35 (d, 2H, *J* = 8.8Hz), 7.17 (d, 2H, *J* = 8.5Hz), 6.87 (d, 1H, *J* = 8.5Hz), 3.68 (s, 2H), 1.89 (s, 2H), 1.41 (s, 6H), 1.39 (s, 6H).

6-Bromo-8-carbaldehyde-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 40**)

Following general procedure M and using 6-bromo-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane](**Intermediate 36**, 2.3g, 8.65mmol), anhydrous dichloromethane (25mL), 1M solution (8.65mL, 8.65mmol) of titanium tetrachloride in dichloromethane and α,α-dichloromethyl ether (1.09g, 9.52mmol) followed by flash column chromatography using 10% ethyl acetate in hexane as the eluent, the title compound was obtained as a yellow solid (2.06g, 81%).

¹H NMR (300 MHz, CDCl₃): δ 10.20 (s, 1H), 7.69 (d, 1H, *J* = 2.6Hz), 7.58 (d, 1H, *J* = 2.6Hz), 1.92 (s, 2H), 1.40 (s, 6H), 1.09-1.04 (m, 2H), 0.73-0.69 (m, 2H).

6-Bromo-3,4-dihydro-4,4-dimethyl-8-vinylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 41**)

Following general procedure N and using A solution of methylenetriphenyl phosphorane [generated from methyl triphenylphosphonium bromide (7g, 20mmol) and 1.6M solution of *n*-butyl lithium in hexanes (11.8mL, 19mmol)], 6-bromo-8-carbonyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane](**Intermediate 40**, 2.06g, 7mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 1-2% ethyl acetate in hexane as the eluent, the title compound was obtained as a clear oil (1.36g, 66%).

¹H NMR (300 MHz, CDCl₃): δ 7.36 (d, 1H, *J* = 2.3Hz), 7.28 (d, 1H, *J* = 2.6Hz), 6.80 (dd, 1H, *J* = 11.1, 17.9Hz), 5.63 (dd, 1H, *J* = 1.2, 17.9Hz), 5.19 (dd, 1H, *J* = 1.2, 11.1Hz), 1.84 (s, 2H), 1.35 (s, 6H), 0.97 (t, 2H, *J* = 6.3Hz), 0.62 (d, 1H, *J* = 5.3Hz), 0.60 (d, 1H, *J* = 6.2Hz).

1 6-Bromo-8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-
2 2,1'-cyclopropane] (**Intermediate 42**)

3 Following general procedure O and using A 6-bromo-3,4-dihydro-4,4-
4 dimethyl-8-vinylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate**
5 **41**, 1.36g, 4.6mmol), a solution of diazomethane in diethyl ether and
6 palladium (II)acetate (~30mg) followed by flash column chromatography over
7 silica gel (230-400 mesh) using hexane as the eluent, the title compound was
8 obtained as a clear oil (1.38g, 100%).

9 ¹H NMR (300 MHz, CDCl₃): δ 7.19 (d, 1H, *J* = 2.2Hz), 6.71 (d, 1H, *J* =
10 2.2Hz), 1.99-1.92 (m, 1H), 1.87 (s, 2H), 1.35 (s, 6H), 1.00-0.95 (m, 2H), 0.90-
11 0.82 (m, 2H), 0.65-0.54 (m, 4H).

12 8-Cyclopropyl-3,4-dihydro-4,4-dimethyl-6-(trimethylsilyl)ethynylspiro[2H-
13 1-benzopyran-2,1'-cyclopropane] (**Intermediate 43**)

14 Following general procedure D and 6-bromo-8-cyclopropyl-3,4-
15 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]
16 (**Intermediate 42**, 0.74g, 2.4mmol), (trimethylsilyl)acetylene (4mL, 28mmol),
17 triethyl amine (8mL), anhydrous tetrahydrofuran, copper(I)iodide (0.050g,
18 0.26mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.15g,
19 0.22mmol), followed by flash column chromatography over silica gel (230-
20 400 mesh) using 1-2% ethyl acetate in hexane as the eluent, the title compound
21 was obtained as an oil (0.62g, 80%).

22 ¹H NMR (300 MHz, CDCl₃): δ 7.28 (d, 1H, *J* = 1.9Hz), 6.77 (d, 1H, *J* =
23 1.9Hz), 2.03-1.94 (m, 1H), 1.91 (s, 2H), 1.40 (s, 6H), 1.05-0.98 (m, 2H), 0.95-
24 0.83 (m, 2H), 0.69-0.59 (m, 4H), 0.27 (s, 9H).

25 8-Cyclopropyl-6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-
26 2,1'-cyclopropane] (**Intermediate 44**)

27 Following general procedure E, and 8-cyclopropyl-3,4-dihydro-4,4-
28 dimethyl-6-(trimethylsilyl)ethynylspiro[2H-1-benzopyran-2,1'-
29 cyclopropane] (**Intermediate 43**, 0.62g, 1.9mmol), methanol and potassium

1 carbonate (0.5g, 3.6mmol) followed by flash column chromatography over
2 silica gel (230-400 mesh) using 1-2% ethyl acetate in hexane as the eluent, the
3 title compound was obtained as an oil (0.5g, 100%).

4 ¹H NMR (300 MHz, CDCl₃): δ 7.30 (d, 1H, *J* = 1.8Hz), 6.80 (d, 1H, *J* =
5 2.0Hz), 2.97 (s, 1H), 2.04-1.95 (m, 1H), 1.91 (s, 2H), 1.39 (s, 6H), 1.20-0.90
6 (m, 2H), 0.90-0.84 (m, 2H), 0.75-0.58 (m, 4H).

7 Benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-
8 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (Compound 47,
9 **General Formula 1)**

10 Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-
11 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]
12 (**Intermediate 44**, 0.11g, 0.43mmol), methyl-4-iodo phenyl acetate (**Reagent**
13 **B**, 0.114g, 0.41mmol), triethyl amine (5mL), tetrahydrofuran (3mL),
14 copper(I)iodide (0.025g, 0.13mmol) and
15 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), the title
16 compound was obtained as a clear oil (0.096g, 56%).

17 ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, 2H, *J* = 8.0Hz), 7.31 (d, 1H, *J* =
18 1.9Hz), 7.24 (d, 2H, *J* = 8.2Hz), 6.81 (d, 1H, *J* = 1.9Hz), 3.69 (s, 3H), 3.62 (s,
19 2H), 2.04-1.95 (m, 1H), 1.90 (s, 2H), 1.39 (s, 6H), 1.03-0.99 (m, 2H), 0.90-
20 0.83 (m, 2H), 0.68-0.59 (m, 4H).

21 Benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-
22 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 48, General
23 **Formula 1)**

24 Following general procedure L and using benzeneacetic acid, 4-[(8-
25 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-
26 cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 47**, 0.96g, 0.24mmol),
27 5mL of methanol and 1M sodium hydroxide solution (2mL) followed by flash
28 column chromatography over silica gel (230-400 mesh) using 15% methanol

1 in dichloromethane as the eluent, the title compound was obtained as a solid
2 (0.084g, 91%).
3 ¹H NMR (300 MHz, CDCl₃): δ 10.27 (br s, 1H), 7.46 (d, 2H, *J* = 8.2Hz), 7.30
4 (d, 1H, *J* = 1.8Hz), 7.23 (d, 2H, *J* = 8.2Hz), 6.80 (d, 1H, *J* = 1.5Hz), 3.63 (s,
5 2H), 2.07-1.94 (m, 1H), 1.89 (s, 2H), 1.39 (s, 6H), 1.03-0.98 (m, 2H), 0.89-
6 0.82 (m, 2H), 0.73-0.59 (m, 4H).

7 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
8 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid methyl ester
9 **(Compound 49, General Formula 1)**

10 Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-
11 dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]
12 (**Intermediate 44**, 0.125g, 0.5mmol), methyl-2-fluoro-4-iodo phenyl acetate
13 (**Reagent H**, 0.14g, 0.5mmol), triethyl amine (3mL), tetrahydrofuran (3mL),
14 copper(I)iodide (0.020g, 0.1mmol) and
15 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) followed
16 by preparative normal phase HPLC using 10% ethyl acetate in hexane as the
17 mobile phase, the title compound was obtained (0.096g, 46%).

18 ¹H NMR (300 MHz, CDCl₃): δ 7.30 (d, 1H, *J* = 2.1Hz), 7.26-7.18 (m, 3H),
19 6.80 (d, 1H, *J* = 1.8Hz), 3.71 (s, 3H), 3.67 (s, 2H), 2.04-1.94 (m, 1H), 1.90 (s,
20 2H), 1.40 (s, 6H), 1.18-0.99 (m, 2H), 0.90-0.83 (m, 2H), 0.68-0.59 (m, 4H).

21 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
22 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid (**Compound 50,**
23 **General Formula 1)**

24 Following general procedure L and using 4-[(8-cyclopropyl-3,4-
25 dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-
26 yl)ethynyl]-2-fluoro-benzeneacetic acid methyl ester (**Compound 49**, 0.096g,
27 0.23mmol), 5mL of methanol and 1M sodium hydroxide solution (2mL)
28 followed by flash column chromatography over silica gel (230-400 mesh)

1 using 15% methanol in dichloromethane as the eluent, the title compound was
2 obtained as a solid (0.093g, 100%).

3 ¹H NMR (300 MHz, CDCl₃): δ 9.50 (br s, 1H), 7.27 (d, 1H, *J* = 2.1Hz), 7.24-
4 7.15 (m, 3H), 6.77 (d, 1H, *J* = 1.5Hz), 3.67 (s, 2H), 2.01-1.91 (m, 1H), 1.87 (s,
5 2H), 1.36 (s, 6H), 1.01-0.96 (m, 2H), 0.87-0.80 (m, 2H), 0.65-0.56 (m, 4H).

6 Benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-
7 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (Compound 51,
8 **General Formula 1**)

9 Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-
10 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]
11 (**Intermediate 44**, 0.05g, 0.2mmol), ethyl-4-iodo-benzoate (**Reagent A**,
12 0.055g, 0.2mmol), triethyl amine (3mL), tetrahydrofuran(3mL),
13 copper(I)iodide(0.020g, 0.1mmol) and
14 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol), the title
15 compound was obtained (0.06g, 75%).

16 ¹H NMR (300 MHz, CDCl₃): δ 8.00 (d, 2H, *J* = 8.2Hz), 7.55 (d, 2H, *J* =
17 8.2Hz), 7.33 (d, 1H, *J* = 1.8Hz), 6.83 (d, 1H, *J* = 2.1Hz), 4.38 (q, 2H, *J* =
18 7.1Hz), 2.04-1.95 (m, 1H), 1.91 (s, 2H), 1.40 (s, 6H), 1.40 (t, 3H, *J* = 7.0Hz),
19 1.05-0.95 (m, 2H), 0.91-0.84 (m, 2H), 0.69-0.61 (m, 4H).

20 Benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-
21 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 52, **General**
22 **Formula 1**)

23 Following general procedure L and using benzoic acid, 4-[(8-
24 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-
25 cyclopropane]-6-yl)ethynyl]-ethyl ester (**Compound 51**, 0.06g, 0.15mmol),
26 5mL of methanol and 1M sodium hydroxide solution (2mL) followed by
27 preparative reverse phase HPLC using 10% water in acetonitrile as the mobile
28 phase, the title compound was obtained as a solid (0.040g, 72%).

1 ¹H NMR (300 MHz, CDCl₃): δ 8.08 (d, 2H, *J* = 8.8Hz), 7.60 (d, 2H, *J* =
2 8.8Hz), 7.34 (d, 1H, *J* = 1.9Hz), 6.84 (d, 1H, *J* = 1.9Hz), 2.05-1.96 (m, 1H),
3 1.92 (s, 2H), 1.41 (s, 6H), 1.05-0.95 (m, 2H), 0.92-0.83 (m, 2H), 0.75-0.60 (m,
4 4H).

5 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
6 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzoic acid methyl ester (Compound
7 **53, General Formula 1)**

8 Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-
9 dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]
10 (**Intermediate 44**, 0.03g, 0.11mmol), methyl-2-fluoro-4-iodo-benzoate
11 (**Reagent G**, 0.025g, 0.09mmol), triethyl amine (3mL), tetrahydrofuran(3mL),
12 copper(I)iodide(0.020g, 0.1mmol) and
13 dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed by
14 preparative normal phase HPLC using 10% ethyl acetate in hexane as the
15 mobile phase, the title compound was obtained as a white solid (0.019g, 40%).
16 ¹H NMR (300 MHz, CDCl₃): δ 7.97 (t, 1H, *J* = 7.8Hz), 7.34 (d, 1H, *J* =
17 1.9Hz), 7.32-7.25 (m, 2H), 6.83 (d, 1H, *J* = 1.9Hz), 3.95 (s, 3H), 2.06-1.96 (m,
18 1H), 1.93 (s, 2H), 1.42 (s, 6H), 1.06-1.02 (m, 2H), 0.91-0.86 (m, 2H), 0.71-
19 0.61 (m, 4H).

20 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
21 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzoic acid (Compound 54, General
22 **Formula 1)**

23 Following general procedure L and using 4-[(8-cyclopropyl-3,4-
24 dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-
25 yl)ethynyl]-2-fluoro-benzoic acid methyl ester (**Compound 53**, 0.019g,
26 0.047mmol), 5mL of methanol and 1M sodium hydroxide solution (2mL)
27 followed by preparative reverse phase HPLC using 10% water in acetonitrile
28 as the mobile phase, the title compound was obtained as a solid (0.01g, 56%).

1 ¹H NMR (300 MHz, CDCl₃): δ 7.99 (t, 1H, *J* = 8.0Hz), 7.36 -7.28 (m, 3H),
2 6.83 (d, 1H, *J* = 1.9Hz), 2.18-1.95 (m, 1H), 1.92 (s, 2H), 1.41 (s, 6H), 1.06-
3 1.01 (m, 2H), 0.96-0.83 (m, 2H), 0.76-0.60 (m, 4H).

4 8-Acetyl-6-bromo-2,2,4,4-tetramethyl chroman (Intermediate 45)

5 A stirred, cooled (ice bath) suspension of aluminum chloride (0.99g,
6 7.46mmol) in anhydrous dichloromethane (20 mL) was treated with acetyl
7 chloride (0.58g, 7.46mmol). After 5 minutes, a solution of 6-bromo-2,2,4,4-
8 tetramethyl chroman (1g, 3.73mmol) in dichloromethane was added. The
9 reaction was allowed to warm to ambient temperature and stirred for 2h. The
10 reaction mixture was then poured into ice containing 10% hydrochloric acid
11 and extracted with diethyl ether (x2). The combined organic phase was
12 washed with saturated aqueous sodium bicarbonate solution, dried over
13 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue which
14 was subjected to flash column chromatography over silica gel (230-400 mesh)
15 using 5% ethyl acetate in hexane as the eluent to afford the title compound as a
16 pale yellow oil (0.95g, 83%). It was used as such for the next step without any
17 characterization.

18 6-Bromo-8-ethyl-2,2,4,4-tetramethyl chroman (Intermediate 46)

19 A stirred, cooled (ice bath) solution of 8-acetyl-6-bromo-2,2,4,4-
20 tetramethyl chroman (Intermediate 45, 0.95g, 3.1mmol) in trifluoroacetic
21 acid (10mL) was treated with triethylsilane (10mL) and the resulting reaction
22 mixture was allowed to warm to ambient temperature and stirred overnight.
23 The volatiles were distilled off in *vacuo* and the residue was diluted with water
24 and extracted with hexane (x2). The combined organic phase was dried over
25 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil which
26 was subjected to flash column chromatography over silica gel (230-400 mesh)
27 using hexane as the eluent to afford the title compound as a clear oil,
28 contaminated with a small amount of triethylsilane (0.51g, 56%).

1 ¹H NMR (300 MHz, CDCl₃): δ 7.23 (d, 1H, *J* = 2.3Hz), 7.08 (d, 1H, *J* =
2 2.3Hz), 2.58 (q, 2H, *J* = 7.6Hz), 1.81 (s, 2H), 1.34 (s, 6H), 1.33 (s, 6H), 1.17
3 (t, 3H, *J* = 7.6Hz).
4 8-Ethyl-6-trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate**
5 **47**)

6 Following general procedure D and using 6-bromo-8-ethyl-2,2,4,4-
7 tetramethyl chroman (**Intermediate 46**, 0.5g, 1.61mmol),
8 (trimethylsilyl)acetylene (1.57g, 16.1mmol), triethyl amine (8mL), anhydrous
9 tetrahydrofuran (10mL), copper(I)iodide (0.025g, 0.13mmol) and
10 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), followed
11 by flash column chromatography over silica gel (230-400 mesh) using 5%
12 ethyl acetate in hexane as the eluent, the title compound was obtained as an oil
13 (0.137g, 27%).

14 ¹H NMR (300 MHz, CDCl₃): δ 7.27 (d, 1H, *J* = 2.1Hz), 7.10 (d, 1H, *J* =
15 2.1Hz), 2.55 (q, 2H, *J* = 7.6Hz), 1.81 (s, 2H), 1.33 (s, 6H), 1.32 (s, 6H), 1.15
16 (t, 3H, *J* = 7.6Hz), 0.24 (s, 9H).

17 8-Ethyl-6-ethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 48**)

18 Following general procedure E and using 8-ethyl-6-
19 trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 47**,
20 0.137g, 0.44mmol), methanol and potassium carbonate (0.1g, 0.72mmol)
21 followed by flash column chromatography over silica gel (230-400 mesh)
22 using 5% ethyl acetate in hexane as the eluent, the title compound was
23 obtained as an oil (0.066g, 62%).

24 ¹H NMR (300 MHz, CDCl₃): δ 7.33 (d, 1H, *J* = 2.2Hz), 7.15 (d, 1H, *J* =
25 1.6Hz), 2.99 (s, 1H), 2.59 (q, 2H, *J* = 7.6Hz), 1.84 (s, 2H), 1.37 (s, 6H), 1.35
26 (s, 6H), 1.19 (t, 3H, *J* = 7.6Hz).

27 [4-(8-Ethyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid
28 methyl ester (**Compound 55, General Formula 8**)

1 Following general procedure F and using 8-ethyl-6-ethynyl-2,2,4,4-
2 tetramethylchroman (**Intermediate 48**, 0.033g, 0.136mmol), methyl-4-iodo
3 phenyl acetate (**Reagent B**, 0.034g, 0.12mmol), triethyl amine (2mL),
4 tetrahydrofuran (2mL), copper(I)iodide (0.025g, 0.13mmol) and
5 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) the title
6 compound was obtained (0.035g, 73%).
7 ¹H NMR (300 MHz, CDCl₃): δ 7.49 (d, 2H, *J* = 7.9Hz), 7.35 (d, 1H, *J* =
8 1.8Hz), 7.26 (d, 2H, *J* = 7.9Hz), 7.18 (d, 1H, *J* = 1.9Hz), 3.72 (s, 3H), 3.65 (s,
9 2H), 2.61 (q, 2H, *J* = 7.5Hz), 1.85 (s, 2H), 1.38 (s, 12H), 1.21 (t, 3H, *J* =
10 7.5Hz).

11 [4-(8-Ethyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid
12 (**Compound 56, General Formula 8**)

13 Following general procedure L and using [4-(8-ethyl-2,2,4,4-
14 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid methyl ester
15 (**Compound 55**, 0.035g, 0.1mmol), 5mL of methanol and 1M sodium
16 hydroxide solution (1mL) followed by preparative reverse phase HPLC using
17 10% water in acetonitrile as the mobile phase, the title compound was
18 obtained as a solid (0.11g, 25%).

19 ¹H NMR (300 MHz, CDCl₃): δ 7.48 (d, 2H, *J* = 8.0Hz), 7.33 (d, 1H, *J* =
20 1.9Hz), 7.25 (d, 2H, *J* = 8.0Hz), 7.15 (d, 1H, *J* = 1.9Hz), 3.65 (s, 2H), 2.59 (q,
21 2H, *J* = 7.5Hz), 1.83 (s, 2H), 1.35 (s, 12H), 1.18 (t, 3H, *J* = 7.4Hz).

22 Spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-
23 3,4-dihydro-4,4-dimethyl- (**Intermediate 49**)

24 Following general procedure R and using 6-bromo-8-cyclopropyl-3,4-
25 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]
26 (**Intermediate 42**, 0.45g, 1.48mmol), anhydrous tetrahydrofuran (5mL), 1.7M
27 solution of *tert*-butyl lithium solution in pentane (1.74mL, 2.96mmol) and
28 carbon dioxide generated from dry ice, followed by flash column
29 chromatography over silica gel (230-400 mesh) using 50% ethyl acetate in

1 hexane as the eluent, the title compound was obtained as a white solid (0.34g,
2 85%).

3 ¹H NMR (300 MHz, CDCl₃): δ 12.43 (br s, 1H), 7.94 (d, 1H, *J* = 2.1Hz), 7.42
4 (d, 1H, *J* = 1.8Hz), 2.06-1.96 (m, 1H), 1.92 (s, 2H), 1.42 (s, 6H), 1.12-0.97 (m,
5 2H), 0.95-0.81 (m, 2H), 0.77-0.60 (m, 4H).

6 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-
7 3,4-dihydro-4,4-dimethyl-, 4-(*tert*-butoxycarbonylmethyl)phenyl ester
8 **(Compound 57, General Formula 1)**

9 A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic
10 acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl- (**Intermediate 49**, 0.06g,
11 0.22mmol) in anhydrous dichloromethane (5mL) was treated with *tert*-butyl-4-
12 hydroxy phenyl acetate (**Reagent E**, 0.05g, 0.22mmol) followed by 1-(3-
13 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.11g, 0.22mmol)
14 and 4-dimethylaminopyridine (0.028g, 0.22mmol). The resulting solution was
15 stirred at ambient temperature overnight. The reaction mixture was subjected
16 to flash column chromatography over silica gel (230-400 mesh) using 7%
17 ethyl acetate in hexane as the eluent to afford the title compound as a clear oil
18 that solidified on standing (0.048g, 48%).

19 ¹H NMR (300 MHz, CDCl₃): δ 7.91 (d, 1H, *J* = 2.1Hz), 7.41 (d, 1H, *J* =
20 1.8Hz), 7.24 (d, 2H, *J* = 8.8Hz), 7.05 (d, 2H, *J* = 8.5Hz), 3.46 (s, 2H), 1.97-
21 1.90 (m, 1H), 1.87 (s, 2H), 1.37 (s, 9H), 1.36 (s, 6H), 1.04-0.90 (m, 2H), 0.87-
22 0.75 (m, 2H), 0.65-0.56 (m, 4H).

23 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-
24 3,4-dihydro-4,4-dimethyl-, 4-(carboxymethyl)phenyl ester (**Compound 58**,
25 **General Formula 1**)

26 A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic
27 acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl-, 4-(*tert*-
28 butoxycarbonylmethyl)phenyl ester (**Compound 57**, 0.048g, 0.105mmol) was
29 treated with 2mL of trifluoroacetic acid and stirred at ambient temperature for

1 2h. The trifluoroacetic acid was distilled off under reduced pressure and the
2 residue was subjected to preparative reverse phase HPLC using 10% water in
3 acetonitrile as the mobile phase to afford the title compound as a white solid
4 (0.029g, 55%).

5 ¹H NMR (300 MHz, CDCl₃): δ 7.99 (d, 1H, *J* = 2.2Hz), 7.48 (d, 1H, *J* =
6 1.9Hz), 7.34 (d, 2H, *J* = 8.5Hz), 7.16 (d, 2H, *J* = 8.5Hz), 3.67 (s, 2H), 2.07-
7 1.97 (m, 1H), 1.95 (s, 2H), 1.44 (s, 6H), 1.09-1.04 (m, 2H), 0.93-0.85 (m, 2H),
8 0.79-0.64 (m, 4H).

9 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-
10 3,4-dihydro-4,4-dimethyl-, 3-(*tert*-butoxycarbonylmethyl)phenyl ester
11 **(Compound 59, General Formula 1)**

12 A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic
13 acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl- (**Intermediate 49**, 0.05g,
14 0.18mmol) in anhydrous dichloromethane (5mL) was treated with *tert*-butyl-3-
15 hydroxy phenyl acetate (**Reagent F**, 0.04g, 0.18mmol) followed by 1-(3-
16 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.029g, 0.1mmol)
17 and 4-dimethylaminopyridine (0.022g, 0.18mmol). The resulting solution was
18 stirred at ambient temperature overnight. The reaction mixture was subjected
19 to flash column chromatography over silica gel (230-400 mesh) using 7%
20 ethyl acetate in hexane as the eluent to afford the title compound as a clear oil
21 that solidified on standing (0.020g, 23%).

22 ¹H NMR (300 MHz, CDCl₃): δ 7.98 (d, 1H, *J* = 1.9Hz), 7.48 (d, 1H, *J* =
23 2.2Hz), 7.38 (t, 1H, *J* = 7.7Hz), 7.19-7.11 (m, 3H), 3.68 (s, 2H), 2.05-1.94 (m,
24 1H), 1.95 (s, 2H), 1.44 (s, 15H), 1.09-1.04 (m, 2H), 0.96-0.82 (m, 2H), 0.73-
25 0.64 (m, 4H).

26 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-
27 3,4-dihydro-4,4-dimethyl-, 3-(carboxymethyl)phenyl ester (**Compound 60**,
28 **General Formula 1**)

1 A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic
2 acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl-, 3-(*tert*-
3 butoxycarbonylmethyl)phenyl ester (**Compound 59**, 0.020g, 0.04mmol) was
4 treated with 2mL of trifluoroacetic acid and stirred at ambient temperature for
5 2h. The trifluoroacetic acid was distilled off under reduced pressure and the
6 residue was subjected to preparative reverse phase HPLC using 10% water in
7 acetonitrile as the mobile phase to afford the title compound as a white solid
8 (0.0125g, 62%).

9 ¹H NMR (300 MHz, CDCl₃): δ 7.99 (d, 1H, *J* = 2.1Hz), 7.49 (d, 1H, *J* =
10 2.1Hz), 7.36 (t, 1H, *J* = 7.8Hz), 7.18-7.08 (m, 3H), 3.56 (s, 2H), 2.06-1.95 (m,
11 1H), 1.95 (s, 2H), 1.45 (s, 6H), 1.09-1.05 (m, 2H), 0.96-0.84 (m, 2H), 0.74-
12 0.65 (m, 4H).

13 6-Bromo-4,4-dimethyl-1,2,3,4-tetrahydro-quinoline-1-carbaldehyde
14 (**Intermediate 50**)

15 A solution of 6-bromo-4,4-dimethyl-1,2,3,4-tetrahydroquinoline,
16 available in accordance with United States Patent No. 5,089,509, the
17 specification of which is incorporated herein by reference (1.8g, 7.5mmol) in
18 10mL of formic acid was refluxed for 3h. The reaction mixture was then
19 cooled to ambient temperature and poured into ice-cold saturated aqueous
20 sodium bicarbonate solution and extracted with diethyl ether (x2). The
21 combined organic phase was dried over anhydrous sodium sulfate, filtered and
22 evaporated in *vacuo* to a residue which was subjected to flash column
23 chromatography over silica gel (230-400 mesh) using 15-25% ethyl acetate in
24 hexane as the eluent to afford the title compound as a pale yellow solid (1.8g,
25 90%).

26 ¹H NMR (300 MHz, CDCl₃): δ 8.71 (s, 1H), 7.45 (d, 1H, *J* = 2.2Hz), 7.28 (dd,
27 1H, *J* = 2.2, 8.5Hz), 6.98 (d, 1H, *J* = 8.5Hz), 3.78 (t, 2H, *J* = 6.3Hz), 1.74 (t,
28 2H, *J* = 6.3Hz), 1.28 (s, 6H).

1 6-Bromo-1-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline

2 **(Intermediate 51)**

3 A stirred, cooled (0°C) solution of 6-bromo-4,4-dimethyl-1,2,3,4-
4 tetrahydro-quinoline-1-carbaldehyde (**Intermediate 50**, 21.8, 6.7mmol) in
5 anhydrous tetrahydrofuran (20mL) under argon was treated with titanium
6 tetra-*iso*-propoxide (2.15mL, 7.39mmol) followed by 3M solution of ethyl
7 magnesium bromide in diethyl ether (5.6mL, 16.8mmol) and the reaction
8 mixture was then heated at 50°C overnight. It was then cooled in an ice-bath,
9 quenched with saturated aqueous ammonium chloride solution and extracted
10 with diethyl ether (x2). The combined organic phase was dried over anhydrous
11 sodium sulfate, filtered over celite and evaporated in *vacuo* to residue which
12 was subjected to flash column chromatography over silica gel (230-400 mesh)
13 using 5% ethyl acetate in hexane as the eluent to afford the title compound as
14 an oil (1.2g, 64%).

15 ¹H NMR (300 MHz, CDCl₃): δ 7.24 (d, 1H, *J* = 2.5Hz), 7.12 (dd, 1H, *J* = 2.2,
16 8.8Hz), 7.01 (d, 1H, *J* = 8.8Hz), 3.20 (t, 2H, *J* = 6.0Hz), 2.27-2.20 (m, 1H),
17 1.68 (t, 2H, *J* = 5.9Hz), 1.24 (s, 3H), 1.23 (s, 3H), 0.83-0.77 (m, 2H), 0.60-
18 0.55 (m, 2H).

19 1-Cyclopropyl-6-trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-tetrahydro-
20 quinoline (Intermediate 52)

21 Following general procedure D and using 6-bromo-1-cyclopropyl-4,4-
22 dimethyl-1,2,3,4-tetrahydro quinoline (**Intermediate 51**, 0.8g, 2.86mmol),
23 (trimethylsilyl)acetylene (5mL, 35mmol), triethyl amine (10mL), anhydrous
24 tetrahydrofuran, copper(I)iodide (0.080g, 0.42mmol) and
25 dichlorobis(triphenylphosphine)palladium(II) (0.240g, 0.34mmol), the title
26 compound was obtained as an oil (0.67g, 79%).

27 ¹H NMR (300 MHz, CDCl₃): δ 7.33 (d, 1H, *J* = 1.8Hz), 7.22 (dd, 1H, *J* = 2.1,
28 8.5Hz), 7.06 (d, 1H, *J* = 8.5Hz), 3.27 (t, 2H, *J* = 5.9Hz), 2.37-2.31 (m, 1H),

1 1.70 (t, 2H, $J = 6.0\text{Hz}$), 1.28 (s, 6H), 0.89-0.82 (m, 2H), 0.66-0.60 (m, 2H),
2 0.28 (s, 9H).

3 1-Cyclopropyl-6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline:
4 **(Intermediate 53)**

5 Following general procedure E and using 1-cyclopropyl-6-
6 trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline
7 **(Intermediate 52, 0.40g, 1.34mmol)**, methanol and potassium carbonate
8 (0.2g, 1.47mmol) followed by flash column chromatography over silica gel
9 (230-400 mesh) using 2% ethyl acetate in hexane as the eluent, the title
10 compound was obtained as an oil (0.17g, 56%).

11 ^1H NMR (300 MHz, CDCl_3): δ 7.38 (d, 1H, $J = 2.1\text{Hz}$), 7.27 (dd, 1H, $J = 2.1$,
12 8.5Hz), 7.11 (d, 1H, $J = 8.5\text{Hz}$), 3.30 (t, 2H, $J = 6.0\text{Hz}$), 3.02 (s, 1H), 2.40-
13 2.34 (m, 1H), 1.74 (t, 2H, $J = 6.0\text{Hz}$), 1.30 (s, 6H), 0.93-0.85 (m, 2H), 0.70-
14 0.63 (m, 2H).

15 4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)-
16 benzoic acid ethyl ester **(Compound 61, General Formula 7)**

17 Following general procedure F and using 1-cyclopropyl-6-ethynyl-4,4-
18 dimethyl-1,2,3,4-tetrahydro quinoline **(Intermediate 53, 0.11g, 0.43mmol)**,
19 ethyl-4-iodo-benzoate **(Reagent A, 0.11g, 0.9mmol)**, triethyl amine (3mL),
20 tetrahydrofuran(3mL), copper(I)iodide(0.02g, 0.1mmol) and
21 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) followed
22 by flash column chromatography over silica gel (230-400 mesh) using 5-10%
23 ethyl acetate in hexane as the eluent, the title compound was obtained (0.05g,
24 31%).

25 ^1H NMR (300 MHz, CDCl_3): δ 7.99 (d, 2H, $J = 8.2\text{Hz}$), 7.54 (d, 2H, $J =$
26 8.2Hz), 7.37 (d, 1H, $J = 2.1\text{Hz}$), 7.26 (dd, 1H, $J = 2.1$, 8.5Hz), 7.10 (d, 1H, $J =$
27 8.8Hz), 4.37 (q, 2H, $J = 7.1\text{Hz}$), 3.28 (t, 2H, $J = 6.0\text{Hz}$), 2.40-2.33 (m, 1H),
28 1.71 (t, 2H, $J = 5.8\text{Hz}$), 1.40 (t, 3H, $J = 7.0\text{Hz}$), 1.27 (s, 6H), 0.94-0.82 (m,
29 2H), 0.65-0.60 (m, 2H).

1 4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl-ethynyl)-
2 benzoic acid (Compound 62, General Formula 7)

3 Following general procedure L and using 4-(1-cyclopropyl-4,4-
4 dimethyl-1,2,3,4-tetrahydro-quinolin-6-ylethynyl)-benzoic acid ethyl ester
5 (**Compound 61**, 0.05g, 0.13mmol), 5mL of ethanol and 5M sodium hydroxide
6 solution (2mL) followed by recrystallization from hot ethyl acetate, the title
7 compound was obtained as a solid (0.030g, 64%).

8 ¹H NMR (300 MHz, DMSO-d₆): δ 7.92 (d, 2H, J = 8.2Hz), 7.57 (d, 2H, J =
9 8.2Hz), 7.33 (d, 1H, J = 1.9Hz), 7.23 (dd, 1H, J = 1.9, 8.5Hz), 7.06 (d, 1H, J =
10 8.8Hz), 3.25 (t, 2H, J = 5.8Hz), 2.41-2.34 (m, 1H), 1.64 (t, 2H, J = 5.6Hz),
11 1.21 (s, 6H), 0.87-0.81 (m, 2H), 0.59-0.54 (m, 2H).

12 [4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-
13 ethynyl)phenyl] acetic acid methyl ester (Compound 63, General Formula
14 7)

15 Following general procedure F and using 1-cyclopropyl-6-ethynyl-4,4-
16 dimethyl-1,2,3,4-tetrahydro quinoline (**Intermediate 53**, 0.05g, 0.22mmol),
17 methyl-4-iodo-phenyl acetate (**Reagent B**, 0.055g, 0.2mmol), triethyl amine
18 (5mL), tetrahydrofuran, copper(I)iodide(0.025g, 0.13mmol) and
19 dichlorobis(triphenylphosphine)palladium(II) (0.75g, 0.11mmol) followed
20 preparative normal phase HPLC using 10 % ethyl acetate in hexane as the
21 mobile phase, the title compound was obtained (0.089g, 100%).

22 ¹H NMR (300 MHz, CDCl₃): δ 7.47 (d, 2H, J = 8.8Hz), 7.45 (d, 1H, J =
23 1.8Hz), 7.35-7.22 (m, 2H), 7.10 (d, 2H, J = 8.8Hz), 3.70 (s, 3H), 3.63 (s, 2H),
24 3.27 (t, 2H, J = 6.0Hz), 2.37-2.31 (m, 1H), 1.71 (t, 2H, J = 6.0Hz), 1.27 (s,
25 6H), 0.89-0.81 (m, 2H), 0.65-0.60 (m, 2H).

26 [4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)-2-
27 fluoro-phenyl] acetic acid ethyl ester (Compound 64, General Formula 7)

28 Following general procedure F and using 1-cyclopropyl-6-ethynyl-4,4-
29 dimethyl-1,2,3,4-tetrahydro quinoline (**Intermediate 53**, 0.11g, 0.49mmol),

1 ethyl-2-fluoro-4-iodo-phenyl acetate (**Reagent C**, 0.11g, 0.9mmol), triethyl
2 amine (3mL), tetrahydrofuran(3mL), copper(I)iodide(0.06g, 0.32mmol) and
3 dichlorobis(triphenylphosphine)palladium(II) (0.25g, 0.36mmol) followed by
4 flash column chromatography over silica gel (230-400 mesh) using 10 % ethyl
5 acetate in hexane as the eluent, the title compound was obtained (0.1g, 51%).
6 ¹H NMR (300 MHz, CDCl₃): δ 7.34 (d, 1H, *J* = 2.1Hz), 7.25-7.17 (m, 3H),
7 7.09 (d, 2H, *J* = 8.8Hz), 4.17 (q, 2H, *J* = 7.1Hz), 3.65 (s, 2H), 3.27 (t, 2H, *J* =
8 6.0Hz), 2.38-2.31 (m, 1H), 1.69 (t, 2H, *J* = 6.0Hz), 1.27 (s, 6H), 1.25 (t, 3H, *J* =
9 = 7.1Hz), 0.88-0.81 (m, 2H), 0.65-0.59 (m, 2H).

10 N-(4-Bromophenyl)-N-methyl-3-methyl-2-butenamide (**Intermediate 54**)

11 3,3-Dimethylacryloyl chloride (3mL, 27mmol) was added to a solution
12 of 4-bromo-N-methyl-aniline (4.55g, 25mmol) in 150mL of dichloromethane
13 followed after 5 minutes by triethyl amine (5mL, 33mmol). After 2.5h at
14 ambient temperature, the reaction mixture was washed with water and the
15 organic phase was dried over anhydrous sodium sulfate and evaporated in
16 vacuo to afford the title product as a brown oil in quantitative yield.
17 ¹H-NMR (300 MHz, CDCl₃): δ 1.71 (s, 3H), 2.11(s, 3H), 3.28(s, 3H), 5.47(s,
18 1H), 7.05(d, *J* = 8.5Hz, 2H), 7.50(d, *J* = 8.2Hz, 2H).

19 6-Bromo-1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline (**Intermediate 55**)

20 N-(4-bromophenyl)-N-methyl-3-methyl-2-butenamide
21 (**Intermediate 54**, 6.42g, 24mmol) was heated to 130°C and aluminum
22 chloride (5g, 37.4mmol) was added in portions over 0.5h. The reaction
23 mixture was stirred for 1 hour at the same temperature and then cooled to
24 room temperature. Ice was added cautiously to the solid, followed by ~200mL
25 of iced water. The reaction mixture was then extracted with ether (x2) and
26 dichloromethane (x1) and the combined organic phase was dried over
27 anhydrous magnesium sulfate and evaporated in *vacuo* to yield a brown solid.
28 The solid was treated with hexane-dichloromethane and filtered to afford 1.7g
29 of product. The mother liquor was evaporated and purified by flash column

1 chromatography on silica gel (230-400 mesh) to afford 2.9g of the title
2 compound as a solid (total 72%).
3 ¹H-NMR (300 MHz, CDCl₃): δ 1.29(s, 6H), 2.49(s, 2H), 3.36(s, 3H), 6.87(d, *J*
4 = 8.2Hz, 1H), 7.36(dd, *J* = 2.0, 8.5Hz, 1H), 7.39(d, *J* = 2.0Hz, 1H).

5 6-Bromo-1,4,4-trimethylspiro[2H-1-1,2,3,4-tetrahydroquinoline-2,1'-
6 cyclopropane] (**Intermediate 56**)

7 A stirred, cooled (-78°C) 3M solution of ethyl magnesium bromide in
8 ether (8.1mL, 24.25mmol) under argon was treated with anhydrous
9 tetrahydrofuran (20mL) followed by a solution of titanium tetra-*iso*-propoxide
10 (3.15mL, 10.2mmol) in tetrahydrofuran (10mL). A solution of 6-bromo-1,4,4-
11 trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline (**Intermediate 55**, 2.6g,
12 9.7mmol) was cannulated into the reaction mixture and the solution was
13 allowed to warm to room temperature overnight. It was then cooled in an ice-
14 bath, quenched with saturated aqueous ammonium chloride solution, filtered
15 over celite and the aqueous phase was extracted with diethyl ether (x2). The
16 combined organic phase was dried over anhydrous magnesium sulfate, filtered
17 and evaporated in *vacuo* to afford an orange oil. Flash column
18 chromatography over silica gel (230-400 mesh) using 2-4% ethyl acetate in
19 hexane as the eluent afforded the title compound as an oil which was ~70%
20 pure (1.7g, 63%) and 0.5g of recovered starting material.

21 ¹H-NMR (300 MHz, CDCl₃): δ 0.58(t, *J* = 6.0Hz, 2H), 0.91(t, *J* = 6.0Hz, 2H),
22 1.35 (s, 6H), 1.70(s, 2H), 2.68 (s, 3H), 6.59 (d, *J* = 8.8Hz, 1H), 7.16(dd, *J* =
23 2.3, 8.8Hz, 1H), 7.33(d, *J* = 2.3Hz, 1H).

24 1,4,4-Trimethyl-6-(trimethylsilyl)ethynylspiro[2H-1-1,2,3,4-
25 tetrahydroquinoline-2,1'-cyclopropane] (**Intermediate 57**)

26 Following general procedure D and using 6-bromo-1,4,4-
27 trimethylspiro[2H-1-1,2,3,4-tetrahydroquinoline-2,1'-cyclopropane]
28 (**Intermediate 56**, 0.56g, 2mmol), (trimethylsilyl)acetylene (1.13mL, 8mmol),
29 triethyl amine (4mL), anhydrous tetrahydrofuran (5mL), copper(I)iodide

1 (0.08g, 0.4mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.28g,
2 0.4mmol), followed by flash column chromatography over silica gel (230-400
3 mesh) using hexane-2% ethyl acetate in hexane as the eluent, the title
4 compound was obtained as an oil (0.42g, 70%).

5 ¹H NMR (300 MHz, CDCl₃): δ 0.023(s, 9H), 0.33(t, *J* = 6.1Hz, 2H), 0.71(t, *J*
6 = 6.1Hz, 2H), 1.10(s, 6H), 1.45(s, 2H), 2.41 (s, 3H), 6.31(d, *J* = 8.5Hz, 1H),
7 6.96 (dd, *J* = 2.1, 8.5Hz, 1H), 7.10(d, *J* = 2.1Hz, 1H).

8 Benzoic acid, 4-[(1,4,4-trimethylspiro[2H-1-1,2,3,4-tetrahydroquinoline-2,1'-
9 cyclopropane]-6-yl)ethynyl]-ethyl ester (Compound 65, General Formula 1)

10 Following general procedure E and using a solution of 1,4,4-trimethyl-
11 6-(trimethylsilyl)ethynylspiro[2H-1-1,2,3,4-tetrahydroquinoline-2,1'-
12 cyclopropane] (Intermediate 57, 0.416g, 1.4mmol), methanol (10mL), ethyl
13 acetate (2mL) and potassium carbonate (1.08g, mmol) a silyl deprotected
14 acetylenic intermediate was obtained which was used directly for the next step
15 (0.25g, 79%). Following general procedure F and using part of the acetylenic
16 intermediate obtained as above (0.11g, 0.5mmol), ethyl-4-iodo benzoate
17 (Reagent A, 0.112g, 0.4mmol), triethyl amine (1mL), tetrahydrofuran
18 (2.5mL), copper(I)iodide (0.050g, 0.26mmol) and
19 tetrakis(triphenylphosphine)palladium(0)(0.096g, 0.17mmol) followed by
20 flash column chromatography over silica gel (230-400 mesh) using 8% ethyl
21 acetate in hexane as the eluent and preparative HPLC on Partisil 10 silica
22 column using 10% ethyl acetate in hexane as the mobile phase, the title
23 compound was obtained as a yellow oil (0.048g, 26%).

24 ¹H-NMR (300 MHz, CDCl₃): δ 0.60 (t, *J* = 6.1Hz, 2H), 0.99(t, *J* = 6.1Hz, 2H),
25 1.37(s, 6H), 1.42(t, *J* = 7.0Hz, 3H), 1.73(s, 2H), 2.68(s, 3H), 4.40 (q, *J* =
26 7.0Hz, 2H), 6.61(d, *J* = 8.8Hz, 1H), 7.28 (dd, *J* = 2.1, 8.5Hz, 1H), 7.42 (d, *J* =
27 2.1Hz, 1H), 7.57(d, *J* = 8.2Hz, 2H), 8.01(d, *J* = 8.2Hz, 2H).

28 Benzoic acid, 4-[(1,4,4-trimethylspiro[2H-1-1,2,3,4-tetrahydroquinoline-2,1'-
29 cyclopropane]-6-yl)ethynyl]- (Compound 66, General Formula 1)

1 Following general procedure I and using benzoic acid, 4-[(1,4,4-
2 trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-cyclopropane]-6-
3 yl)ethynyl]-ethyl ester (**Compound 65**, 0.03g, 0.08mmol), ethanol (2mL),
4 tetrahydrofuran (2mL) and 1M aqueous sodium hydroxide solution (1mL), the
5 title compound was obtained as a yellow solid (0.020g, 67%).
6 ¹H-NMR (300 MHz, CD₃COCD₃): δ 0.60 (t, *J* = 5.8Hz, 2H), 1.03(t, *J* = 5.8Hz,
7 2H), 1.34(s, 6H), 1.74(s, 2H), 2.69(s, 3H), 6.60(d, *J* = 8.5Hz, 1H), 7.23 (dd, *J*
8 = 2.0, 8.4Hz, 1H), 7.39 (d, *J* = 2.0Hz, 1H), 7.58(d, *J* = 8.2Hz, 2H), 8.01(d, *J*
9 = 8.2Hz, 2H).

10 Esterification Methods:

11 Method A:

12 The carboxylic acid was combined with a solution of the desired
13 alcohol and concentrated sulfuric acid (20 to 1 v/v) and the resulting mixture
14 or solution (0.75 to 1.0 M) heated to reflux overnight. The solution was
15 cooled to room temperature, diluted with Et₂O, and washed with H₂O,
16 saturated aqueous NaHCO₃, and saturated aqueous NaCl before being dried
17 over MgSO₄. Concentration of the dry solution under reduced pressure
18 afforded the desired carboxylic ester of sufficient purity to be used directly in
19 the next reaction.

20 Method B:

21 To a solution (0.67 to 1.0M) of the carboxylic acid in acetone was
22 added 1.1equivalents of the desired alkyl halide and 1.0 equivalents of solid
23 potassium carbonate. The resulting mixture was heated to reflux for 2h and
24 then allowed to stir at room temperature overnight. The mixture was filtered
25 and the filtrate concentrated under reduced pressure. The product was isolated
26 from the residue by column chromatography using silica gel as the solid phase.

27 Method C:

28 A solution (1M) of the carboxylic acid in thionyl chloride was heated at

1 reflux until analysis of a reaction aliquot by IR spectroscopy showed the
2 absence of the aryl carboxylic acid carbonyl band (1705 - 1680 cm^{-1}). The
3 solution was cooled to room temperature and concentrated under reduced
4 pressure to give the crude acyl chloride.

5 The acyl chloride was dissolved in CH_2Cl_2 and the resulting solution
6 (0.5 to 0.75M) treated with 1.1 equivalents the desired alcohol and 2.0
7 equivalents of pyridine. After stirring overnight at room temperature the
8 solution was diluted with Et_2O and washed with H_2O , 10% aqueous HCl ,
9 saturated aqueous NaHCO_3 , and saturated aqueous NaCl before being dried
10 over Na_2SO_4 . Concentration of the dry solution under reduced pressure
11 followed by column chromatography afforded the desired ester.

12 GENERAL PROCEDURE 1 (preparation of Enol ethers):

13 A solution (0.35 M) of the aryl ester in anhydrous THF was cooled to 0
14 $^\circ\text{C}$ and treated with 1.0 equivalents of Tebbe's Reagent ($[\mu\text{-chloro-}\mu\text{-}$
15 $\text{methylene[bis(cyclopentadienyl)titanium]-dimethylaluminum}]$ 0.5 M in
16 toluene). After 30 minutes the solution was warmed to room temperature and
17 stirred for 30 minutes before being carefully added to a 0.1 N NaOH solution
18 at 0 $^\circ\text{C}$. This mixture was treated with hexanes and the solids removed by
19 filtration through a pad of Celite. The solids were washed with hexanes and
20 the filtrate passed through a second pad of Celite to remove any newly formed
21 solids. The organic layer was dried (Na_2SO_4) and concentrated under reduced
22 pressure. The desired enol ether was isolated from the residue by column
23 chromatography using 1-2% of Et_3N added to the eluant. (note: prolonged
24 exposure of the product to the column can result in hydrolysis and formation
25 of the corresponding methyl ketone.)

26 GENERAL PROCEDURE 2 (cyclopropanation of the enol ethers):

27 To a solution (0.3 M) of the enol ether in anhydrous Et_2O was added
28 2.0 equivalent of Et_2Zn (as a solution in hexanes) and 2.0 equivalents of CH_2I_2 .

1 The resulting solution was heated to reflux until analysis of a reaction aliquot
2 (by TLC or ^1H NMR) indicated that all of the starting enol ether had been
3 consumed. (note: Additional equal amounts of Et_2Zn and CH_2I_2 can be added
4 to drive the reaction to completion.) Upon cooling to room temperature the
5 reaction was carefully quenched by the addition of saturated aqueous NH_4Cl .
6 The resulting mixture is extracted with Et_2O and the combined organic layers
7 washed with H_2O and saturated aqueous NaCl before being dried over Na_2SO_4
8 and concentrated under reduced pressure. The product is isolated from the
9 residue by column chromatography.

10 1-Bromo-4-(1-methoxyvinyl)-benzene: (**Intermediate 58**)

11 Using General Procedure 1; methyl 4-bromo-benzoate (600.0 mg, 2.78
12 mmols), and 5.6 mL of Tebbe's Reagent (794.0 mg, 2.78 mmols) afforded
13 420.0 mg (70%) of the title compound as a colorless oil after column
14 chromatography (100% hexanes).
15 ^1H NMR (CDCl_3) δ : 7.48 - 7.45 (4H, m), 4.64 (1H, d, $J = 2.9$ Hz), 4.23 (1H, d,
16 $J = 2.9$ Hz), 3.73 (3H, s).

17 1-Bromo-4-(1-methoxycyclopropyl)-benzene (**Intermediate 59**)

18 Using General Procedure 2; 1-bromo-4-(1-methoxyvinyl)-benzene
19 (**Intermediate 58**, 410.0 mg, 1.92 mmols), Et_2Zn (711.3 mg, 5.76 mmols),
20 and CH_2I_2 (1.54 g, 5.76 mmols) in 4.0 mL Et_2O afforded 300.0 mg (69%) of
21 the title compound as a colorless oil after chromatography (0-3% EtOAc -
22 hexanes).

23 ^1H NMR (CDCl_3) δ : 7.46 (2H, d, $J = 8.5$ Hz), 7.18 (2H, d, $J = 8.5$ Hz), 3.21
24 (3H, s), 1.19 (2H, m), 0.94 (2H, m).

25 [4-(1-Methoxycyclopropyl)-phenylethynyl]-trimethylsilane (**Intermediate**
26 **60**)

27 Using General Procedure D; 1-bromo-4-(1-methoxycyclopropyl)-
28 benzene (**Intermediate 59**, 300.0 mg, 1.32 mmol) in triethylamine (4 mL) and

1 anhydrous tetrahydrofuran (4 mL) was treated with copper(I)iodide (93.0 mg,
2 0.13 mmol) and then sparged with argon for 5 minutes. Trimethylsilyl
3 acetylene (1.39 g, 14.2 mmols) was then added followed by
4 dichlorobis(triphenylphosphine)palladium(II) (93.0 mg, 0.13 mmol). The
5 resulting reaction mixture was heated to 70 °C for 60h. The title compound
6 (286.0 mg, 90%) was isolated by chromatography (0 - 3% EtOAc - hexanes).
7 ¹H NMR (CDCl₃) δ: 7.35 (2H, d, J = 7.2 Hz), 7.14 (2H, d, J = 7.2 Hz), 3.14
8 (3H, s), 1.14 (2H, m), 0.88 (2H, m), 0.17 (9H, s).

9 1-Ethynyl-4-(1-methoxycyclopropyl)-benzene (Intermediate 61)

10 Using General Procedure E; [4-(1-methoxycyclopropyl)-
11 phenylethynyl]-trimethylsilane (Intermediate 60, 285.0 mg, 1.18 mmols) in
12 methanol (10mL) was treated with potassium carbonate (100.0 mg, 0.72
13 mmol) and stirred overnight at ambient temperature. The crude alkyne (220
14 mg, 100%) was used directly in the next reaction.
15 ¹H NMR (CDCl₃) δ: 7.46 (2H, d, J = 8.2 Hz), 7.24 (2H, d, J = 8.2 Hz), 3.23
16 (3H, s), 3.06 (1H, s), 1.22 (2H, m), 0.98 (2H, m).

17 Ethyl 4-[4-(1-methoxycyclopropyl)-phenylethynyl]-benzoate (Compound 67,

18 **General Formula 2)**

19 Using General Procedure F; 1-ethynyl-4-(1-methoxycyclopropyl)-
20 benzene (Intermediate 61, 100.0 mg, 0.47 mmol) and ethyl-4-iodo benzoate
21 (Reagent A, 141.0 mg, 0.51 mmol) in triethyl amine (6 mL) was treated with
22 copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon for 5 minutes.
23 Dichlorobis(triphenylphosphine)palladium(II) (109 mg, 0.16 mmol) was added
24 and the reaction mixture was stirred overnight at room temperature. Column
25 chromatography (2-5% EtOAc - hexanes) afforded 135.0 mg (90%) of the title
26 compound as an orange solid.
27 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.8 Hz), 7.52
28 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 8.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 3.25

1 (3H, s), 1.40 (3H, t, J = 7.1 Hz), 1.23 (2H, m), 1.00 (2H, m).

2 Methyl {4-[4-(1-methoxycyclopropyl)-phenylethynyl]-phenyl}-acetate

3 **(Compound 68, General Formula 2)**

4 Using General Procedure F; 1-ethynyl-4-(1-methoxycyclopropyl)-
5 benzene (**Intermediate 61**, 120.0 mg, 0.56 mmol) and methyl-(4-iodophenyl)-
6 acetate (**Reagent B**, 154.0 mg, 0.56 mmol) in triethyl amine (6 mL) was
7 treated with copper(I)iodide (35.0 mg, 0.19 mmol) and sparged with argon for
8 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (130 mg, 0.19
9 mmol) was added and the reaction mixture was stirred overnight at room
10 temperature. Column chromatography (2-8% EtOAc - hexanes) afforded
11 140.0 mg (78%) of the title compound as an orange solid.

12 ¹H NMR (CDCl₃) δ: 7.50 (4H, d, J = 8.1 Hz), 7.28 (4H, d, J = 8.1 Hz), 3.76
13 (3H, s), 3.64 (2H, s), 3.25 (3H, s), 1.22 (2H, m), 0.99 (2H, m).

14 4-[4-(1-Methoxycyclopropyl)-phenylethynyl]-benzoic acid (**Compound 69**,
15 **General Formula 2**)

16 Using General Procedure I; a solution of ethyl 4-[4-(1-
17 methoxycyclopropyl)-phenylethynyl]-benzoate (**Compound 67**, 110.0 mg,
18 0.34 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with
19 NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and stirred
20 overnight at room temperature. Work-up afforded 85.0 mg (86%) of the title
21 compound as an orange solid.

22 ¹H NMR (CDCl₃) δ: 8.05 (2H), 7.66 (2H), 7.56 (2H, d, J = 8.5 Hz), 7.35 (2H,
23 d, J = 8.6 Hz), 3.22 (3H, s), 1.21 (2H, m), 1.01 (2H, m).

24 {4-[4-(1-Methoxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid
25 **(Compound 70, General Formula 2)**

26 Using General Procedure I; a solution of methyl {4-[4-(1-
27 methoxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 68**, 100.0
28 mg, 0.31 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated

1 with NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and
2 stirred overnight at room temperature. Work-up afforded 80.0 mg (84%) of
3 the title compound as an orange solid.
4 ¹H NMR (CDCl₃) δ: 7.49 (4H), 7.27 (4H), 3.66 (2H, s), 3.25 (3H, s), 1.22 (2H,
5 m), 0.99 (2H, m).

6 Isopropyl 4-bromobenzoate (Intermediate 62)

7 Using General Esterification Procedure A; 4-bromobenzoic acid (1.50
8 g, 7.46 mmols) was combined with isopropyl alcohol to give 1.76 g (97%) of
9 the title compound as a colorless oil.

10 ¹H NMR (CDCl₃) δ: 7.90 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz),
11 5.24 (1H, septet, J = 6.2 Hz), 1.37 (6H, d, J = 6.2 Hz).

12 1-Bromo-4-(1-isopropoxyvinyl)-benzene (Intermediate 63)

13 Using General Procedure 1; isopropyl 4-bromobenzoate (**Intermediate**
14 **62**, 780.0 mg, 3.20 mmols) and 6.4 mL of Tebbe's Reagent (910.7 mg, 3.20
15 mmols) afforded 328.0 mg (43%) of the title compound as a colorless oil after
16 column chromatography (100% hexanes).

17 ¹H NMR (CDCl₃) δ: 7.46 (4H, m), 4.66 (1H, d, J = 2.6 Hz), 4.40 (1H, septet, J
18 = 6.2 Hz), 4.21 (1H, d, J = 2.6 Hz), 1.34 (6H, d, J = 6.2 Hz).

19 1-Bromo-4-(1-isopropoxycyclopropyl)-benzene (Intermediate 64)

20 Using General Procedure 2; 1-bromo-4-(1-isopropoxyvinyl)-benzene
21 (**Intermediate 63**, 328.0 mg, 1.36 mmols), Et₂Zn (335.9 mg, 2.72 mmols),
22 and CH₂I₂ (728.0 mg, 2.72 mmols) in 4.0 mL Et₂O afforded 240.0 mg (70%)
23 of the title compound as a colorless oil after chromatography (3% EtOAc -
24 hexanes).

25 ¹H NMR (CDCl₃) δ: 7.43 (2H, d, J = 8.5 Hz), 7.27 (2H, d, J = 8.5 Hz), 3.70
26 (1H, septet, J = 6.2 Hz), 1.18 (2H, m), 1.06 (6H, d, J = 6.2 Hz), 0.91 (2H, m).

27 [4-(1-Isopropoxycyclopropyl)-phenylethynyl]-trimethylsilane (Intermediate
28 **65)**

1 Using General Procedure D; 1-bromo-4-(1-isopropoxycyclopropyl)-
2 benzene (**Intermediate 64**, 240.0 mg, 0.94 mmol) in triethylamine (8 mL) was
3 treated with copper(I)iodide (18.0 mg, 0.094 mmol) and then sparged with
4 argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was then
5 added followed by dichlorobis-(triphenylphosphine)palladium(II) (66.0 mg,
6 0.094 mmol). The resulting reaction mixture was heated to 70 °C for 5 days.
7 The title compound (250.0 mg, 98%) was isolated by chromatography (0 - 3%
8 EtOAc - hexanes) as an orange oil.
9 ¹H NMR (CDCl₃) δ: 7.41 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 3.70
10 (1H, septet, J = 6.2 Hz), 1.18 (2H, m), 1.05 (6H, d, J = 6.2 Hz), 0.93 (2H, m),
11 0.94 (9H, s).

12 1-Ethynyl-4-(1-isopropoxycyclopropyl)-benzene (**Intermediate 66**)

13 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-
14 phenylethynyl]-trimethylsilane (**Intermediate 65**, 260.0 mg, 0.96 mmol) in
15 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72
16 mmol) and stirred overnight at ambient temperature. The crude alkyne (220
17 mg, 100%) was used directly in the next reaction.
18 ¹H NMR (CDCl₃) δ: 7.45 (2H, d, J = 8.8 Hz), 7.35 (2H, d, J = 8.8 Hz), 3.72
19 (1H, septet, J = 6.2 Hz), 3.06 (1H, s), 1.20 (2H, m), 1.07 (6H, d, J = 6.2 Hz),
20 0.95 (2H, m).

21 Ethyl 4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-benzoate (**Compound**
22 **71, General Formula 2**)

23 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-
24 benzene (**Intermediate 66**, 114.0 mg, 0.57 mmol) and ethyl-4-iodo benzoate
25 (**Reagent A**, 731.0 mg, 0.63 mmol) in triethylamine (8 mL) was treated with
26 copper(I)iodide (36.0 mg, 0.19 mmol) and sparged with argon for 5 minutes.
27 Dichlorobis(triphenylphosphine)palladium(II) (133 mg, 0.19 mmol) was added
28 and the reaction mixture was stirred overnight at room temperature. Column

1 chromatography (2-4% EtOAc - hexanes) afforded 151.0 mg (76%) of the title
2 compound as an orange solid.

3 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 7.6 Hz), 7.58 (2H, d, J = 7.6 Hz), 7.50
4 (2H, d, J = 7.8 Hz), 7.39 (2H, d, J = 7.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 3.74
5 (1H, septet, J = 6.2 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.22 (2H, m), 1.08 (6H, d, J =
6 6.2 Hz), 0.97 (2H, m).

7 Methyl {4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetate
8 **(Compound 72, General Formula 2)**

9 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-
10 benzene (**Intermediate 66**, 95.0 mg, 0.45 mmol) and methyl-(4-iodophenyl)-
11 acetate (**Reagent B**, 131.0 mg, 0.45 mmol) in triethylamine (6 mL) was treated
12 with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon for 5
13 minutes. Dichlorobis(triphenylphosphine)palladium(II) (111 mg, 0.16 mmol)
14 was added and the reaction mixture was stirred overnight at room temperature.
15 Column chromatography (2-8% EtOAc - hexanes) afforded 110.0 mg (70%)
16 of the title compound as an orange oil.

17 ¹H NMR (CDCl₃) δ: 7.20 (4H), 7.08 (2H, d, J = 7.0 Hz), 6.97 (2H, d, J = 7.9
18 Hz), 3.45 (1H, septet, J = 6.2 Hz), 3.41 (3H, s), 3.35 (2H, s), 0.91 (2H, m),
19 0.79 (6H, d, J = 6.2 Hz), 0.68 (2H, m).

20 4-[4-(1-Isopropoxycyclopropyl)-phenylethynyl]-benzoic acid (**Compound**
21 **73, General Formula 2**)

22 Using General Procedure I; a solution of ethyl 4-[4-(1-
23 isopropoxycyclopropyl)-phenylethynyl]-benzoate (**Compound 71**, 110.0 mg,
24 0.32 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with
25 NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred
26 overnight at room temperature. Work-up afforded 89.0 mg (88%) of the title
27 compound as a yellow solid.

28 ¹H NMR (CDCl₃) δ: 8.06 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.2 Hz), 7.55

1 (2H, d, J = 8.2 Hz), 7.46 (2H, d, J = 8.2 Hz), 3.73 (1H, septet, J = 6.2 Hz), 1.18
2 (2H, m), 1.04 (6H, d, J = 6.2 Hz), 0.99 (2H, m).

3 {4-[4-(1-Isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid

4 **(Compound 74, General Formula 2)**

5 Using General Procedure I; a solution of methyl {4-[4-(1-
6 isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 72**, 80.0
7 mg, 0.23 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated
8 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and
9 stirred overnight at room temperature. Work-up afforded 48.0 mg (56%) of
10 the title compound as a solid.

11 ¹H NMR (CDCl₃) δ: 7.20 (2H, d, J = 8.2 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.09
12 (2H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.2 Hz), 3.46 (1H, septet, J = 6.2 Hz), 3.37
13 (2H, s), 0.92 (2H, m), 0.79 (6H, d, J = 6.2 Hz), 0.67 (2H, m).

14 Benzyl 4-bromobenzoate (Intermediate 67)

15 Using General Esterification Method B; 4-bromobenzoic acid (2.01 g,
16 10.0 mmols), benzyl bromide (1.89 g, 11.1 mmols), and K₂CO₃ (1.40 g, 10.0
17 mmols) afforded 2.33 g (80%) of the title compound as a colorless solid after
18 column chromatography (3-10% EtOAc - hexanes).

19 ¹H NMR (CDCl₃) δ: 7.89 (2H, d, J = 8.5 Hz), 7.52 (2H, d, J = 8.5 Hz), 7.43 -
20 7.31 (5H), 5.33 (2H, s).

21 1-Bromo-4-(1-benzyloxyvinyl)-benzene (Intermediate 68)

22 Using General Procedure 1; benzyl 4-bromobenzoate (**Intermediate**
23 **67**, 920.0 mg, 3.16 mmols) and 6.3 mL of Tebbe's Reagent (897.0 mg, 3.16
24 mmols) afforded 640.0 mg (70%) of the title compound after column
25 chromatography (100% hexanes).

26 ¹H NMR (CDCl₃) δ: 7.55 - 7.35 (9H), 4.95 (2H, s), 4.73 (1H, d, J = 2.9 Hz),
27 4.34 (1H, d, J = 2.9 Hz).

28 1-Bromo-4-(1-benzyloxycyclopropyl)-benzene (Intermediate 69)

1 Using General Procedure 2; 1-bromo-4-(1-benzyloxyvinyl)-benzene
2 (Intermediate 68, 280.0 mg, 0.97 mmol), Et₂Zn (247.0 mg, 2.0 mmols), and
3 CH₂I₂ (536.0 mg, 2.0 mmols) in 2.0 mL Et₂O afforded 159.0 mg (53%) of the
4 title compound as a colorless solid after chromatography (2-5% EtOAc -
5 hexanes).

6 ¹H NMR (CDCl₃) δ: 7.49 - 7.24 (9H), 4.41 (2H, s), 1.29 (2H, m), 1.00 (2H,
7 m).

8 [4-(1-Benzyloxycyclopropyl)-phenylethynyl]-trimethylsilane (Intermediate
9 70)

10 Using General Procedure D; 1-bromo-4-(1-benzyloxycyclopropyl)-
11 benzene (Intermediate 69, 160.0 mg, 0.53 mmol) in triethylamine (5 mL) was
12 treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then sparged with
13 argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then
14 added followed by dichlorobis-(triphenylphosphine)palladium(II) (37.0 mg,
15 0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d. The
16 title compound (150.0 mg, 83%) was isolated by chromatography (0 - 3%
17 EtOAc - hexanes) as a pale-yellow oil.

18 ¹H NMR (CDCl₃) δ: 7.21 (3H, m), 7.09 - 7.01 (6H, m), 4.18 (2H, s), 1.07 (2H,
19 m), 0.79 (2H, m), 0.02 (9H, s).

20 1-Ethynyl-4-(1-benzyloxycyclopropyl)-benzene (Intermediate 71)

21 Using General Procedure E; [4-(1-benzyloxycyclopropyl)-
22 phenylethynyl]-trimethylsilane (Intermediate 70, 150.0 mg, 0.47 mmols) in
23 methanol (6 mL) was treated with potassium carbonate (100.0 mg, 0.72 mmol)
24 and stirred overnight at ambient temperature. The crude alkyne (115 mg,
25 100%) was used directly in the next reaction.

26 ¹H NMR (CDCl₃) δ: 7.67 - 7.50 (2H, d, J = 8.2 Hz), 7.34 - 7.26 (7H, m), 4.43
27 (2H, s), 3.07 (1H, s), 1.32 (2H, m), 1.04 (2H, m).

28 Ethyl 4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-benzoate (Compound

1 **75, General Formula 2)**

2 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-
3 benzene (**Intermediate 71**, 60.0 mg, 0.24 mmol) and ethyl-4-iodo benzoate
4 (**Reagent A**, 72.0 mg, 0.26 mmol) in triethylamine (4 mL) was treated with
5 copper(I)iodide (17.0 mg, 0.09 mmol) and sparged with argon for 5 minutes.
6 Dichlorobis(triphenylphosphine)palladium(II) (61 mg, 0.09 mmol) was added
7 and the reaction mixture was stirred overnight at room temperature. Column
8 chromatography (2-4% EtOAc - hexanes) afforded 85.0 mg (91%) of the title
9 compound as an orange oil.

10 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.2 Hz), 7.62-7.54 (4H, m), 7.39-7.26
11 (7H, m), 4.47 (2H, s), 4.40 (2H, q, J = 7.1 Hz), 1.42 (3H, t, J = 7.1 Hz), 1.36
12 (2H, m), 1.07 (2H, m).

13 Methyl {4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetate

14 (**Compound 76, General Formula 2)**

15 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-
16 benzene (**Intermediate 71**, 60.0 mg, 0.20 mmol) and methyl-(4-iodophenyl)-
17 acetate (**Reagent B**, 66.0 mg, 0.24 mmol) in triethylamine (5 mL) was treated
18 with copper(I)iodide (15.0 mg, 0.08 mmol) and sparged with argon for 5
19 minutes. Dichlorobis(triphenylphosphine)palladium(II) (56 mg, 0.08 mmol)
20 was added and the reaction mixture was stirred overnight at room temperature.
21 Column chromatography (2-7% EtOAc - hexanes) afforded 64.0 mg (81%) of
22 the title compound as a yellow oil.

23 ¹H NMR (CDCl₃) δ: 7.52-7.47 (4H, m), 7.37-7.25 (9H, m), 4.44 (2H, s), 3.70
24 (3H, s), 3.64 (2H, s), 1.32 (2H, m), 1.06 (2H, m).

25 4-[4-(1-Benzyloxycyclopropyl)-phenylethynyl]-benzoic acid (**Compound 77,**

26 **General Formula 2)**

27 Using General Procedure I; a solution of ethyl 4-[4-(1-
28 benzyloxycyclopropyl)-phenylethynyl]-benzoate (**Compound 75**, 78.0 mg,

1 0.20 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with
2 NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred
3 overnight at room temperature. Work-up afforded 65.0 mg (89%) of the title
4 compound as a solid.

5 ¹H NMR (CDCl₃) δ: 7.97 (2H, d, J = 8.5 Hz), 7.67 (2H, d, J = 8.7 Hz), 7.58
6 (2H, d, J = 8.5 Hz), 7.41-7.28 (7H, m), 4.44 (2H, s), 1.33 (2H, m), 1.12 (2H,
7 m).

8 {4-[4-(1-Benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid
9 **(Compound 78, General Formula 2)**

10 Using General Procedure I; a solution of methyl {4-[4-(1-
11 benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 76**, 45.0
12 mg, 0.11 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated
13 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and
14 stirred overnight at room temperature. Work-up afforded 35.0 mg (81%) of
15 the title compound as a pale-yellow solid.

16 ¹H NMR (CDCl₃) δ: 7.49 (4H, m), 7.37-7.25 (9H, m), 4.44 (2H, s), 3.66 (2H,
17 s), 1.32 (2H, m), 1.05 (2H, m).

18 Benzyl 4-bromo-2-methylbenzoate (Intermediate 72)

19 Using General Esterification Method C; 2-methyl-4-bromo-benzoic
20 acid (2.15 g, 10.0 mmols) was refluxed for 3h with 10 mL SOCl₂. The
21 resulting solution concentrated under reduced pressure and the crude acyl
22 chloride was combined with benzyl alcohol (1.08 g, 10.0mmols) and pyridine
23 (1.6 mL, 20.0 mmols) to give the title compound (2.4 g, 80%) after work-up
24 and column chromatography (2-5% EtOAc - hexanes) as a colorless oil.

25 ¹H NMR (CDCl₃) δ: 7.81 (1H, d, J = 8.5 Hz), 7.41-7.33 (7H, m), 5.32 (2H, s),
26 2.57 (3H, s).

27 4-Bromo-1-(1-benzyloxyvinyl)-2-methylbenzene (Intermediate 73)

28 Using General Procedure 1; benzyl 4-bromo-2-methylbenzoate

1 (Intermediate 72, 840.0 mg, 2.77 mmols) and 5.4 mL of Tebbe's Reagent
2 (788.0 mg, 2.77 mmols) afforded 640.0 mg (76%) of the title compound after
3 column chromatography (100% hexanes).
4 ¹H NMR (CDCl₃) δ: 7.38-7.19 (8H, m), 4.88 (2H, s), 4.45 (1H, d, J = 2.6 Hz),
5 4.25 (2H, d, J = 2.6 Hz), 2.35 (3H, s).

6 4-Bromo-1-(1-benzyloxycyclopropyl)-2-methyl-benzene (Intermediate 74)

7 Using General Procedure 2; 4-bromo-1-(1-benzyloxyvinyl)-2-methyl-
8 benzene (Intermediate 73, 400.0 mg, 1.32 mmols), Et₂Zn (325.0 mg, 2.63
9 mmols), and CH₂I₂ (704.0 mg, 2.63 mmols) in 4 mL Et₂O afforded 380.0 mg
10 (90%) of the title compound as a colorless oil after chromatography (2-5%
11 EtOAc - hexanes).

12 ¹H NMR (CDCl₃) δ: 7.42-7.20 (8H, m), 4.31 (2H, s), 2.58 (3H, s), 1.25 (2H,
13 m), 0.94 (2H, m).

14 [4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-trimethylsilane
15 (Intermediate 75)

16 Using General Procedure D; 4-bromo-1-(1-benzyloxycyclopropyl)-2-
17 methyl-benzene (Intermediate 74, 320.0 mg, 1.00 mmol) in triethylamine (8
18 mL) was treated with copper(I)iodide (19.0 mg, 0.1 mmol) and then sparged
19 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was
20 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (70.0
21 mg, 0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d.
22 The title compound (300.0 mg, 89%) was isolated by chromatography (0 - 2%
23 EtOAc - hexanes).

24 ¹H NMR (CDCl₃) δ: 7.34-7.13 (8H, m), 4.24 (2H, s), 2.52 (3H, s), 1.20 (2H,
25 m), 0.88 (2H, m), 0.25 (9H, s).

26 4-Ethynyl-1-(1-benzyloxycyclopropyl)-2-methyl-benzene (Intermediate 76)

27 Using General Procedure E; [4-(1-benzyloxycyclopropyl)-3-methyl-
28 phenylethynyl]-trimethylsilane (Intermediate 75, 300.0 mg, 0.95 mmols) in

1 methanol (6 mL) was treated with potassium carbonate (120.0 mg, 0.87 mmol)
2 and stirred overnight at ambient temperature. The crude alkyne (185 mg,
3 79%) was used directly in the next reaction.
4 ¹H NMR (CDCl₃) δ: 7.37-7.16 (8H, m), 4.27 (2H, s), 3.07 (1H, s), 2.55 (3H,
5 s), 1.21 (2H, m), 0.92 (2H, m).

6 Ethyl 4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoate
7 **(Compound 79, General Formula 2)**

8 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-
9 methyl-benzene (**Intermediate 76**, 90.0 mg, 0.34 mmol) and ethyl-4-iodo
10 benzoate (**Reagent A**, 95.0 mg, 0.34 mmol) in triethylamine (6 mL) was
11 treated with copper(I)iodide (23.0 mg, 0.12 mmol) and sparged with argon for
12 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (80 mg, 0.11 mmol)
13 was added and the reaction mixture was stirred overnight at room temperature.
14 Column chromatography (2-4% EtOAc - hexanes) afforded 68.0 mg (54%) of
15 the title compound.

16 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.33-
17 7.16 (8H, m), 4.39 (2H, q, J = 7.1 Hz), 4.29 (2H, s), 2.57 (3H, s), 1.40 (3H, t, J
18 = 7.1 Hz), 1.22 (2H, m), 0.93 (2H, m).

19 Methyl {4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-
20 acetate **(Compound 80, General Formula 2)**

21 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-
22 methyl-benzene (**Intermediate 76**, 90.0 mg, 0.34 mmol) and methyl-(4-
23 iodophenyl)-acetate (**Reagent B**, 95.0 mg, 0.34 mmol) in triethylamine (5 mL)
24 was treated with copper(I)iodide (22.0 mg, 0.11 mmol) and sparged with argon
25 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (80 mg, 0.11
26 mmol) was added and the reaction mixture was stirred overnight at room
27 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded 90.0
28 mg (71%) of the title compound as a pale-yellow oil.

1 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.2 Hz), 7.32-7.16 (10H, m), 4.28 (2H,
2 s), 3.70 (3H, s), 3.64 (2H, s), 2.56 (3H, s), 1.22 (2H, m), 0.92 (2H, m).

3 4-[4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid

4 **(Compound 81, General Formula 2)**

5 Using General Procedure I; a solution of ethyl 4-[4-(1-
6 benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoate (**Compound 79**,
7 68.0 mg, 0.17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
8 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)
9 and stirred overnight at room temperature. Work-up afforded 48.0 mg (76%)
10 of the title compound as a solid.

11 ¹H NMR (CDCl₃) δ: 8.10 (2H, d, J = 8.1 Hz), 7.63 (2H, d, J = 8.1 Hz), 7.44-
12 7.16 (8H, m), 4.29 (2H, m), 2.58 (3H, s), 1.24 (2H, m), 0.94 (2H, m).

13 {4-[4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetic acid

14 **(Compound 82, General Formula 2)**

15 Using General Procedure I; a solution of methyl {4-[4-(1-
16 benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetate (**Compound**
17 **80**, 75.0 mg, 0.18 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
18 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
19 and stirred overnight at room temperature. Work-up afforded 30.0 mg (40%)
20 of the title compound.

21 ¹H NMR (CDCl₃) δ: 7.51 (2H, d, J = 8.2 Hz), 7.42 (1H, s), 7.33-7.17 (9H, m),
22 4.36 (2H, s), 3.67 (2H, s), 2.57 (3H, s), 1.23 (2H, m), 0.94 (2H, m).

23 Isopropyl 3-methyl-4-bromobenzoate (Intermediate 77)

24 Using General Esterification Procedure A; 4-bromo-2-methylbenzoic
25 acid (1.6 g, 7.4 mmols) was combined with isopropyl alcohol to give 1.5 g
26 (79%) of the title compound as a colorless oil.

27 ¹H NMR (CDCl₃) δ: 7.76 (1H, d, J = 8.2 Hz), 7.40 (1H, d, J = 7.4 Hz), 7.37
28 (1H, dd, J = 1.4, 8.2 Hz), 5.23 (1H, septet, J = 6.2 Hz), 2.57 (3H, s), 1.37 (6H,

1 d, J = 6.2 Hz).

2 4-Bromo-1-(1-isopropoxyvinyl)-2-methyl-benzene (Intermediate 78)

3 Using General Procedure 1; isopropyl 2-methyl-4-bromobenzoate
4 (**Intermediate 77**, 800.0 mg, 3.11 mmols) and 6.2 mL of Tebbe's Reagent
5 (885.2 mg, 3.11 mmols) afforded 595.0 mg (75%) of the title compound as a
6 colorless oil after column chromatography (100% hexanes).

7 ¹H NMR (CDCl₃) δ: 7.31-7.25 (2H, m), 7.16 (1H, d, J = 8.2 Hz), 4.34 (1H,
8 septet, J = 6.0 Hz), 4.31 (1H, d, J = 2.1 Hz), 4.18 (1H, d, J = 2.1 Hz), 2.33 (3H,
9 s), 1.31 (6H, d, J = 6.0 Hz).

10 4-Bromo-1-(1-isopropoxycyclopropyl)-2-methyl-benzene (Intermediate 79)

11 Using General Procedure 2; 4-bromo-1-(1-isopropoxyvinyl)-2-methyl-
12 benzene (**Intermediate 78**, 389.0 mg, 1.53 mmols), Et₂Zn (376.6 mg, 3.05
13 mmols), and CH₂I₂ (817.0 mg, 3.05 mmols) in 3.0 mL Et₂O afforded 340.0 mg
14 (84%) of the title compound as a colorless oil after chromatography (3%
15 EtOAc - hexanes).

16 ¹H NMR (CDCl₃) δ: 7.33 (1H, d, J = 2.3 Hz), 7.24 (1H, dd, J = 2.3, 8.2 Hz),
17 7.13 (1H, d, J = 8.2 Hz), 3.57 (1H, septet, J = 6.1 Hz), 2.49 (3H, s), 1.00 (2H,
18 m), 0.97 (6H, d, J = 6.1 Hz), 0.82 (2H, m).

19 [4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-trimethylsilane
20 (**Intermediate 80**)

21 Using General Procedure D; 4-bromo-1-(1-isopropoxycyclopropyl)-2-
22 methyl-benzene (**Intermediate 79**, 250.0 mg, 0.95 mmol) in triethylamine (8
23 mL) was treated with copper(I)iodide (19.0 mg, 0.10 mmol) and then sparged
24 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was
25 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (70.0
26 mg, 0.1 mmol). The resulting reaction mixture was heated to 70 °C for 5d.
27 The title compound (250.0 mg, 91%) was isolated by chromatography (0 - 3%
28 EtOAc - hexanes).

1 ¹H NMR (CDCl₃) δ: 7.32-7.17 (3H, m), 3.56 (1H, septet, J = 6.2 Hz), 2.48
2 (3H, s), 1.00 (2H, m), 0.95 (6H, d, J = 6.2 Hz), 0.83 (2H, m), 0.24 (9H, s).
3 4-Ethynyl-1-(1-isopropoxycyclopropyl)-2-methyl-benzene (Intermediate 81)

4 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-3-methyl-
5 phenylethynyl]-trimethylsilane (**Intermediate 80**, 250.0 mg, 0.87 mmol) in
6 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72
7 mmol) and stirred overnight at ambient temperature. The crude alkyne (180
8 mg, 98%) was used directly in the next reaction.

9 ¹H NMR (CDCl₃) δ: 7.32 (1H, s), 7.23 (2H, m), 3.57 (1H, septet, J = 6.2 Hz),
10 3.05 (1H, s), 2.50 (3H, s), 1.11 (2H, m), 0.96 (6H, d, J = 6.2 Hz), 0.83 (2H, m).
11 Ethyl 4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoate
12 (**Compound 83, General Formula 2**)

13 Using General Procedure F; 4-ethynyl-1-(1-isopropoxycyclopropyl)-3-
14 methyl-benzene (**Intermediate 81**, 80.0 mg, 0.13 mmol) and ethyl-4-iodo
15 benzoate (**Reagent A**, 100.0 mg, 0.36 mmol) in triethylamine (5 mL) was
16 treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged with argon for
17 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (91 mg, 0.13
18 mmol) was added and the reaction mixture was stirred overnight at room
19 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded 75.0
20 mg (56%) of the title compound as an orange solid.

21 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.2 Hz), 7.57 (2H, d, J = 8.2 Hz), 7.39
22 (1H, s), 7.29-7.20 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.60 (1H, septet, J = 6.2
23 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.13 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.87 (2H,
24 m).

25 Methyl {4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-
26 acetate (Compound 84, General Formula 2)

27 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-3-
28 methyl-benzene (**Intermediate 81**, 100.0 mg, 0.47 mmol) and methyl-(4-

1 iodophenyl)-acetate (**Reagent B**, 129.0 mg, 0.45 mmol) in triethylamine (6
2 mL) was treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with
3 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (110 mg,
4 0.16 mmol) was added and the reaction mixture was stirred overnight at room
5 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded
6 120.0 mg (71%) of the title compound.

7 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 8.5 Hz), 7.36 (1H, s), 7.29-7.22 (4H, m),
8 3.70 (3H, s), 3.63 (2H, s), 3.60 (1H, septet, J = 6.2 Hz), 2.52 (3H, s), 1.09 (2H,
9 m), 0.97 (6H, d, J = 6.2 Hz), 0.86 (2H, m).

10 4-[4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid
11 (**Compound 85, General Formula 2**)

12 Using General Procedure I; a solution of ethyl 4-[4-(1-
13 isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoate (**Compound 83**,
14 60.0 mg, 0.17 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was
15 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)
16 and stirred overnight at room temperature. Work-up afforded 38.0 mg (69%)
17 of the title compound as a colorless solid.

18 ¹H NMR (d₆-acetone) δ: 8.06 (2H, d, J = 8.5 Hz), 7.66 (2H, d, J = 8.5 Hz),
19 7.42 (1H, s), 7.35 (2H, m), 3.59 (1H, septet, J = 6.2 Hz), 2.52 (3H, s), 1.07
20 (2H, m), 0.93 (6H, d, J = 6.2 Hz), 0.88 (2H, m).

21 {4-[4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetic
22 acid (**Compound 86, General Formula 2**)

23 Using General Procedure I; a solution of methyl {4-[4-(1-
24 isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetate
25 (**Compound 84**, 100.0 mg, 0.28 mmol) in ethanol (3 mL) and tetrahydrofuran
26 (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N
27 aqueous solution) and stirred overnight at room temperature. Work-up
28 afforded 60.0 mg (62%) of the title compound as a colorless solid.

1 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 7.6 Hz), 7.36 (1H, s), 7.25 (4H, m), 3.65
2 (2H, s), 3.60 (1H, septet, J = 6.2 Hz), 2.51 (3H, s), 1.12 (2H, m), 0.97 (6H, d, J
3 = 6.2 Hz), 0.86 (2H, m).

4 2,2-Dimethylpropyl 2-methyl-4-bromobenzoate (**Intermediate 82**)

5 Using General Esterification Method C; 2-methyl-4-bromo-benzoic
6 acid (1.82 g, 8.47 mmols) was refluxed for 3h with 10 mL SOCl₂. The
7 resulting solution was concentrated under reduced pressure and the crude acyl
8 chloride combined with 2,2-dimethylpropanol (0.75 g, 8.47 mmols) and
9 pyridine (1.4 mL, 16.9 mmols) to give the title compound (1.64 g, 68%) after
10 work-up and column chromatography (2-5% EtOAc - hexanes) as a colorless
11 oil.

12 ¹H NMR (CDCl₃) δ: 7.81 (1H, d, J = 8.2 Hz), 7.42 (1H, d, J = 2.0 Hz), 7.39
13 (1H, dd, J = 2.0, 8.2 Hz), 3.99 (2H, s), 2.60 (3H, s), 1.03 (9H, s).

14 4-Bromo-1-[1-(2,2-dimethylpropyloxy)-vinyl]-2-methyl-benzene
15 (**Intermediate 83**)

16 Using General Procedure 1; 2,2-dimethylpropyl 2-methyl-4-
17 bromobenzoate (**Intermediate 82**, 820.0 mg, 2.87 mmols) and 5.8 mL of
18 Tebbe's Reagent (817.0 mg, 2.87 mmols) afforded 800.0 mg (98%) of the title
19 compound as a colorless oil after column chromatography (100% hexanes).

20 ¹H NMR (CDCl₃) δ: 7.32 (1H, d, J = 2.0 Hz), 7.28 (1H, dd, J = 2.0, 8.2 Hz),
21 7.18 (1H, d, J = 8.2 Hz), 4.27 (1H, d, J = 2.1 Hz), 4.10 (1H, d, J = 2.1 Hz),
22 3.43 (2H, s), 2.33 (3H, s), 0.98 (9H, s).

23 4-Bromo-1-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-2-methyl-benzene
24 (**Intermediate 84**)

25 Using General Procedure 2; 4-bromo-1-[1-(2,2-dimethylpropyloxy)-
26 cyclopropyl]-2-methyl-benzene (**Intermediate 83**, 400.0 mg, 1.43 mmols),
27 Et₂Zn (353.2 mg, 2.86 mmols), and CH₂I₂ (760.0 mg, 2.86 mmols) in 3.0 mL
28 Et₂O afforded 370.0 mg (87%) of the title compound as a colorless oil after

1 chromatography (3% EtOAc - hexanes).

2 ¹H NMR (CDCl₃) δ: 7.36 (1H, s), 7.27 (1H, d, J = 8.5 Hz), 7.09 (1H, d, J = 7.9
3 Hz), 2.86 (2H, s), 2.52 (3H, s), 1.08 (2H, m), 0.83 (2H, m), 0.80 (9H, s).

4 [4-[1-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]]-
5 trimethylsilane (Intermediate 84a)

6 Using General Procedure D; 4-bromo-1-[1-(2,2-dimethylpropyloxy)-
7 cyclopropyl]-2-methyl-benzene (**Intermediate 84**, 255.0 mg, 0.86 mmol) in
8 triethylamine (8 mL) was treated with copper(I)iodide (17.0 mg, 0.09 mmol)
9 and then sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g,
10 7.1 mmols) was then added followed by dichlorobis-

11 (triphenylphosphine)palladium(II) (63.0 mg, 0.09 mmol). The resulting
12 reaction mixture was heated to 70 °C for 5d. The title compound (220.0 mg,
13 81%) was isolated by chromatography (1-2% EtOAc - hexanes).

14 ¹H NMR (CDCl₃) δ: 7.30 (1H, s), 7.21 (1H, d, J = 7.6 Hz), 7.12 (1H, d, J = 8.6
15 Hz), 2.80 (2H, s), 2.47 (3H, s), 1.05 (2H, m), 0.82 (2H, m), 0.75 (9H, s), 0.24
16 (9H, s).

17 4-Ethynyl-1-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-2-methyl-benzene
18 (**Intermediate 85**)

19 Using General Procedure E; [4-[1-[1-(2,2-dimethylpropyloxy)-
20 cyclopropyl]]-3-methyl-phenylethynyl]-trimethylsilane (**Intermediate 84a**,
21 220.0 mg, 0.83 mmol) in methanol (10 mL) was treated with potassium
22 carbonate (80.0 mg, 0.58 mmol) and stirred overnight at ambient temperature.
23 The crude alkyne (155 mg, 76%) was used directly in the next reaction.

24 ¹H NMR (CDCl₃) δ: 7.32 (1H, s), 7.24 (1H, d, J = 7.1 Hz), 7.15 (1H, d, J = 7.1
25 Hz), 3.04 (1H, s), 2.83 (2H, s), 2.49 (3H, s), 1.06 (2H, m), 0.83 (2H, m), 0.76
26 (9H, s).

27 Ethyl 4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-
28 benzoate (Compound 87, General Formula 2)

1 Using General Procedure F; 4-ethynyl-1-[1-(2,2-dimethylpropyloxy)-
2 cyclopropyl]-3-methyl-benzene (**Intermediate 85**, 75.0 mg, 0.31 mmol) and
3 ethyl-4-iodo benzoate (**Reagent A**, 86.0 mg, 0.31 mmol) in triethylamine (5
4 mL) was treated with copper(I)iodide (21.0 mg, 0.11 mmol) and sparged with
5 argon for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (78 mg,
6 0.11 mmol) was added and the reaction mixture was stirred overnight at room
7 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded 60.0
8 mg (50%) of the title compound as an orange solid.

9 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.38
10 (1H, s), 7.30 (1H, dd, J = 1.1, 8.0 Hz), 7.20 (1H, d, J = 8.0 Hz), 4.38 (2H, q, J
11 = 7.1 Hz), 2.84 (2H, s), 2.52 (3H, s), 1.40 (3H, t, J = 7.1 Hz), 1.07 (2H, m),
12 0.84 (2H, m), 0.77 (9H, s).

13 Methyl {4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-
14 phenylethynyl]-phenyl}-acetate (**Compound 88, General Formula 2**)

15 Using General Procedure F; 4-ethynyl-1-[1-(2,2-dimethylpropyloxy)-
16 cyclopropyl]-3-methyl-benzene (**Intermediate 85**, 75.0 mg, 0.31 mmol) and
17 methyl-(4-iodophenyl)-acetate (**Reagent B**, 86.0 mg, 0.31 mmol) in
18 triethylamine (6 mL) was treated with copper(I)iodide (21.0 mg, 0.11 mmol)
19 and sparged with argon for 5 minutes.
20 Dichlorobis(triphenylphosphine)palladium(II) (78 mg, 0.11 mmol) was added
21 and the reaction mixture was stirred overnight at room temperature. Column
22 chromatography (2-4% EtOAc - hexanes) afforded 100.0 mg (83%) of the title
23 compound.

24 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 7.9 Hz), 7.36-7.24 (4H, m), 7.18 (1H, d, J
25 = 7.9 Hz), 3.70 (3H, s), 3.63 (2H, s), 2.84 (2H, s), 2.51 (3H, s), 1.07 (2H, m),
26 0.83 (2H, m), 0.77 (9H, s).

27 4-[4-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-
28 benzoic acid (**Compound 89, General Formula 2**)

1 Using General Procedure I; a solution of ethyl 4-[4-[1-(2,2-
2 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-benzoate
3 (**Compound 87**, 60.0 mg, 0.15 mmol) in ethanol (3 mL) and tetrahydrofuran
4 (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N
5 aqueous solution) and stirred overnight at room temperature. Work-up
6 afforded 24.0 mg (43%) of the title compound as a colorless solid.
7 ¹H NMR (CDCl₃) δ: 8.06 (2H, d, J = 7.9 Hz), 7.65 (2H, d, J = 7.9 Hz), 7.42
8 (1H, s), 7.33 (2H, m), 2.89 (2H, s), 2.53 (3H, s), 1.07 (2H, m), 0.90 (2H, m),
9 0.77 (9H, s).

10 {4-[4-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-
11 phenyl}-acetic acid (**Compound 90**, General Formula 2)

12 Using General Procedure I; a solution of methyl {4-[4-[1-(2,2-
13 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-phenyl}-acetate
14 (**Compound 88**, 95.0 mg, 0.24 mmol) in ethanol (3 mL) and tetrahydrofuran
15 (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N
16 aqueous solution) and stirred overnight at room temperature. Work-up
17 afforded 49.0 mg (53%) of the title compound as a colorless solid.
18 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.2 Hz), 7.36 (1H, s), 7.27 (3H, m), 7.18
19 (1H, d, J = 7.9 Hz), 3.66 (2H, s), 2.84 (2H, s), 2.51 (3H, s), 1.07 (2H, m), 0.83
20 (2H, m), 0.77 (9H, s).

21 Benzyl 4-bromo-2-ethyl-benzoate (**Intermediate 86**)

22 Using General Esterification Method B; 4-bromo-2-ethyl-benzoic acid
23 (0.98 g, 4.25 mmols), benzyl bromide (0.80 g, 4.68 mmols), and K₂CO₃ (0.64
24 g, 4.68 mmols) afforded 1.0 g (74%) of the title compound after column
25 chromatography (0-3% EtOAc - hexanes).

26 ¹H NMR (CDCl₃) δ: 7.76 (1H, d, J = 8.5 Hz), 7.41-7.33 (7H, m), 5.32 (2H, s),
27 2.95 (2H, q, J = 7.6 Hz), 1.20 (3H, t, J = 7.6 Hz).

28 4-Bromo-1-(1-benzyloxyvinyl)-2-ethyl-benzene (**Intermediate 87**)

1 Using General Procedure 1; benzyl 4-bromo-2-ethylbenzoate
2 (Intermediate 86, 1.20 g, 3.78 mmols) and 7.6 mL of Tebbe's Reagent (1.08
3 g, 3.78 mmols) afforded 800.0 mg (66%) of the title compound after column
4 chromatography (100% hexanes).

5 ¹H NMR (CDCl₃) δ: 7.37-7.17 (8H, m), 4.88 (2H, s), 4.43 (1H, d, J = 2.1 Hz),
6 4.25 (1H, d, J = 2.1 Hz), 2.71 (2H, q, J = 7.6 Hz), 1.18 (3H, t, J = 7.6 Hz).

7 4-Bromo-1-(1-benzyloxycyclopropyl)-2-ethyl-benzene (Intermediate 88)

8 Using General Procedure 2; 4-bromo-1-(1-benzyloxyvinyl)-2-ethyl-
9 benzene (Intermediate 87, 330.0 mg, 1.04 mmols), Et₂Zn (257.0 mg, 2.08
10 mmols), and CH₂I₂ (557.0 mg, 2.08 mmols) in 4 mL Et₂O afforded 241.0 mg
11 (70%) of the title compound as a colorless oil after chromatography (2-5%
12 EtOAc - hexanes).

13 ¹H NMR (CDCl₃) δ: 7.43-7.15 (8H, m), 4.27 (2H, s), 3.00 (2H, q, J = 7.6 Hz),
14 1.29-1.21 (5H, m), 0.90 (2H, m).

15 [4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-trimethylsilane
16 (Intermediate 89)

17 Using General Procedure D; 4-bromo-1-(1-benzyloxycyclopropyl)-2-
18 ethyl-benzene (Intermediate 88, 220.0 mg, 0.66 mmol) in triethylamine (8
19 mL) was treated with copper(I)iodide (14.0 mg, 0.07 mmol) and then sparged
20 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was
21 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (50.0
22 mg, 0.07 mmol). The resulting reaction mixture was heated to 70 °C for 5d.
23 The title compound was isolated by chromatography (0 - 2% EtOAc -
24 hexanes).

25 ¹H NMR (CDCl₃) δ: 7.41-7.13 (8H, m), 4.24 (2H, s), 2.98 (2H, q, J = 7.6 Hz),
26 1.25 (3H, t, J = 7.6 Hz), 1.20 (2H, m), 0.90 (2H, m), 0.26 (9H, s).

27 4-Ethynyl-1-(1-benzyloxycyclopropyl)-2-ethyl-benzene (Intermediate 90)

28 Using General Procedure E; [4-(1-benzyloxycyclopropyl)-3-ethyl-

1 phenylethynyl]-trimethylsilane (**Intermediate 89**, 240 mg, 0.69 mmol) in
2 methanol (6 mL) was treated with potassium carbonate (10.0 mg, 0.72 mmol)
3 and stirred overnight at ambient temperature. The crude alkyne (190 mg,
4 99%) was used directly in the next reaction. ¹H NMR (CDCl₃) δ: 7.43-7.15
5 (8H, m), 4.27 (2H, s), 3.08 (1H, s), 3.01 (2H, q, J = 7.6 Hz), 1.26 (3H, t, J =
6 7.6 Hz), 1.22 (2H, m), 0.92 (2H, m).

7 Ethyl 4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate
8 (**Compound 91, General Formula 2**)

9 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-
10 ethyl-benzene (**Intermediate 90**, 90.0 mg, 0.33 mmol) and ethyl-4-iodo
11 benzoate (**Reagent A**, 100.0 mg, 0.36 mmol) in triethylamine (5 mL) was
12 treated with copper(I)iodide (21.0 mg, 0.11 mmol) and sparged with argon for
13 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (77 mg, 0.11 mmol)
14 was added and the reaction mixture was stirred overnight at room temperature.
15 Column chromatography (2-4% EtOAc - hexanes) afforded 100.0 mg (72%)
16 of the title compound.
17 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 7.9 Hz), 7.59 (2H, d, J = 7.9 Hz), 7.49
18 (1H, s), 7.36-7.16 (7H, m), 4.38 (2H, q, J = 7.1 Hz), 4.28 (2H, s), 3.04 (2H, q,
19 J = 7.6 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.23 (2H, m),
20 0.94 (2H, m).

21 Methyl {4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-
22 acetate (**Compound 92, General Formula 2**)

23 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-
24 ethyl-benzene (**Intermediate 90**, 107.0 mg, 0.39 mmol) and methyl-(4-
25 iodophenyl)-acetate (**Reagent B**, 110.0 mg, 0.39 mmol) in triethylamine (5
26 mL) was treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged with
27 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (91 mg,
28 0.13 mmol) was added and the reaction mixture was stirred overnight at room

1 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded
2 130.0 mg (79%) of the title compound as a pale-yellow oil.
3 ¹H NMR (CDCl₃) δ: 7.49 (3H, m), 7.32-7.16 (9H, m), 4.28 (2H, s), 3.71 (3H,
4 s), 3.64 (2H, s), 3.03 (2H, q, J = 7.6 Hz), 1.32-1.23 (5H, m), 0.94 (2H, m).

5 4-[4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoic acid

6 **(Compound 93, General Formula 2)**

7 Using General Procedure I; a solution of ethyl 4-[4-(1-
8 benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate (**Compound 91**,
9 100.0 mg, 0.24 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
10 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
11 and stirred overnight at room temperature. Work-up and purification by
12 HPLC (Partisil 10-pac, 10% H₂O/CH₃CN) afforded the title compound as a
13 colorless solid.

14 ¹H NMR (CDCl₃) δ: 8.10 (2H, d, J = 8.5 Hz), 7.64 (2H, d, J = 8.5 Hz), 7.50
15 (1H, s), 7.35-7.16 (7H, m), 4.29 (2H, s), 3.04 (2H, q, J = 7.6 Hz), 1.30 (3H, t, J
16 = 7.6 Hz), 1.25 (2H, m), 0.95 (2H, m).

17 {4-[4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid

18 **(Compound 94, General Formula 2)**

19 Using General Procedure I; a solution of methyl {4-[4-(1-
20 benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetate (**Compound**
21 **92**, 130.0 mg, 0.31 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
22 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
23 and stirred overnight at room temperature. Work-up and purification by
24 HPLC (Partisil 10-pac, 10% H₂O/CH₃CN) afforded the title compound.

25 ¹H NMR (CDCl₃) δ: 7.49 (3H, m), 7.31-7.16 (9H, m), 4.28 (2H, s), 3.66 (2H,
26 s), 3.02 (2H, q, J = 7.6 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.23 (2H, m), 0.94 (2H,
27 m).

28 Isopropyl 2-ethyl-4-bromobenzoate (**Intermediate 91**)

1 Using General Esterification Procedure A; 4-bromo-2-ethyl-benzoic
2 acid (2.25 g, 9.9 mmols) was combined with isopropyl alcohol to give the title
3 compound as a colorless oil after column chromatography (2% EtOAc-
4 hexanes).

5 ^1H NMR (CDCl_3) δ : 7.69 (1H, d, $J = 8.5$ Hz), 7.41 (1H, s), 7.36 (1H, d, $J = 8.5$
6 Hz), 5.23 (1H, septet, $J = 6.2$ Hz), 2.95 (2H, q, $J = 7.6$ Hz), 1.37 (6H, d, $J = 6.2$
7 Hz), 1.23 (3H, t, $J = 7.6$ Hz).

8 4-Bromo-1-(1-isopropoxyvinyl)-2-ethyl-benzene (Intermediate 92)

9 Using General Procedure 1; isopropyl 2-ethyl-4-bromobenzoate
10 (**Intermediate 91**, 1.21 g, 4.46 mmols) and 8.9 mL of Tebbe's Reagent (1.27
11 g, 4.46 mmols) afforded 570.0 mg (75%) of the title compound after column
12 chromatography (100% hexanes).

13 ^1H NMR (CDCl_3) δ : 7.36 (1H, d, $J = 2.0$ Hz), 7.28 (1H, dd, $J = 2.0, 8.0$ Hz),
14 7.17 (1H, d, $J = 8.0$ Hz), 4.39 (1H, septet, $J = 6.2$ Hz), 4.31 (1H, d, $J = 2.1$ Hz),
15 4.26 (1H, d, $J = 2.1$ Hz), 2.73 (2H, q, $J = 7.6$ Hz), 1.35 (6H, d, $J = 6.2$ Hz),
16 1.24 (3H, t, $J = 7.6$ Hz).

17 4-Bromo-1-(1-isopropoxycyclopropyl)-2-ethyl-benzene (Intermediate 93)

18 Using General Procedure 2; 4-bromo-1-(1-isopropoxyvinyl)-2-ethyl-
19 benzene (**Intermediate 92**, 570.0 mg, 2.11 mmols), Et_2Zn (521.0 mg, 4.22
20 mmols), and CH_2I_2 (1.13 g, 4.22 mmols) in 7.0 mL Et_2O afforded 500.0 mg
21 (85%) of the title compound as a colorless oil after chromatography (3%
22 EtOAc - hexanes).

23 ^1H NMR (CDCl_3) δ : 7.39 (1H, d, $J = 2.1$ Hz), 7.25 (1H, dd, $J = 2.1, 8.1$ Hz),
24 7.15 (1H, d, $J = 8.1$ Hz), 3.59 (1H, septet, $J = 6.2$ Hz), 2.97 (2H, q, $J = 7.6$ Hz),
25 1.27 (3H, t, $J = 7.6$ Hz), 1.11 (2H, m), 0.97 (6H, d, $J = 6.2$ Hz), 0.83 (2H, m).

26 [4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-trimethylsilane

27 (**Intermediate 94**)

28 Using General Procedure D; 4-bromo-1-(1-isopropoxycyclopropyl)-2-

1 ethyl-benzene (**Intermediate 93**, 300.0 mg, 1.07 mmol) in triethylamine (8
2 mL) was treated with copper(I)iodide (20.0 mg, 0.11 mmol) and then sparged
3 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was
4 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (75.0
5 mg, 0.11 mmol). The resulting reaction mixture was heated to 70 °C for 5d.
6 The title compound (320.0 mg, 99%) was isolated by chromatography (0 - 2%
7 EtOAc - hexanes) as an orange oil.

8 ¹H NMR (CDCl₃) δ: 7.37-7.21 (3H, m), 3.56 (1H, septet, J = 6.2 Hz), 2.96
9 (2H, q, J = 7.6 Hz), 1.27 (3H, t, J = 7.6 Hz), 1.10 (2H, m), 0.94 (6H, d, J = 6.2
10 Hz), 0.84 (2H, m), 0.25 (9H, s).

11 4-Ethynyl-1-(1-isopropoxycyclopropyl)-2-ethyl-benzene (**Intermediate 95**)

12 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-3-ethyl-
13 phenylethynyl]-trimethylsilane (**Intermediate 94**, 330.0 mg, 1.10 mmols) in
14 methanol (10 mL) was treated with potassium carbonate (150.0 mg, 1.10
15 mmol) and stirred overnight at ambient temperature. The crude alkyne (238
16 mg, 95%) was used directly in the next reaction.

17 ¹H NMR (CDCl₃) δ: 7.40-7.22 (3H, m), 3.59 (1H, septet, J = 6.2 Hz), 3.07
18 (1H, s), 2.97 (2H, q, J = 7.6 Hz), 1.28 (3H, t, J = 7.6 Hz), 1.12 (2H, m), 0.96
19 (6H, d, J = 6.2 Hz), 0.85 (2H, m).

20 Ethyl 4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate

21 (**Compound 95, General Formula 2**)

22 Using General Procedure F; 4-ethynyl-1-(1-isopropoxycyclopropyl)-3-
23 ethyl-benzene (**Intermediate 95**, 108.0 mg, 0.47 mmol) and ethyl-4-iodo
24 benzoate (**Reagent A**, 130.0 mg, 0.47 mmol) in triethylamine (5 mL) was
25 treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon for
26 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (110 mg, 0.16
27 mmol) was added and the reaction mixture was stirred overnight at room
28 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded

1 125.0 mg (71%) of the title compound as an oil.

2 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.46
3 (1H, s), 7.33-7.26 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.62 (1H, septet, J = 6.2
4 Hz), 3.01 (2H, q, J = 7.6 Hz), 1.41 (3H, t, J = 7.1 Hz), 1.31 (3H, t, J = 7.1 Hz),
5 1.14 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.88 (2H, m).

6 Methyl {4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-
7 acetate (Compound 96, General Formula 2)

8 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-3-
9 ethyl-benzene (**Intermediate 95**, 130.0 mg, 0.57 mmol) and methyl-(4-
10 iodophenyl)-acetate (**Reagent B**, 157.0 mg, 0.57 mmol) in triethylamine (5
11 mL) was treated with copper(I)iodide (36.0 mg, 0.19 mmol) and sparged with
12 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (133 mg,
13 0.19 mmol) was added and the reaction mixture was stirred overnight at room
14 temperature. Column chromatography (2-5% EtOAc - hexanes) afforded
15 150.0 mg (70%) of the title compound as an orange oil.

16 ¹H NMR (CDCl₃) δ: 7.50-7.44 (3H, m), 7.27 (4H, m), 3.70 (3H, s), 3.64 (2H,
17 s), 3.62 (1H, septet, J = 6.2 Hz), 3.00 (2H, q, J = 7.6 Hz), 1.30 (3H, t, J = 7.6
18 Hz), 1.13 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.87 (2H, m).

19 4-[4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoic acid
20 (Compound 97, General Formula 2)

21 Using General Procedure I; a solution of ethyl 4-[4-(1-
22 isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate (**Compound 95**,
23 110.0 mg, 0.29 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
24 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
25 and stirred overnight at room temperature. Work-up and isolation by HPLC
26 (partisil 10-pac, 10% H₂O/CH₃CN) afforded the title compound as a colorless
27 solid.

28 ¹H NMR (d₆-acetone) δ: 8.06 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz),

1 7.49 (1H, s), 7.40-7.34 (2H, m), 3.61 (1H, septet, J = 6.2 Hz), 3.01 (2H, q, J =
2 7.6 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.08 (2H, m), 0.93 (6H, d, J = 6.2 Hz), 0.88
3 (2H, m).

4 {4-[4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid
5 **(Compound 98, General Formula 2)**

6 Using General Procedure I; a solution of methyl {4-[4-(1-
7 isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetate (**Compound**
8 **96**, 156.0 mg, 0.41 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
9 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
10 and stirred overnight at room temperature. Work-up and isolation by HPLC
11 (partisil 10-pac, 10% H₂O/CH₃CN) afforded 85.0 mg (57%) of the title
12 compound.

13 ¹H NMR (CDCl₃) δ: 7.54-7.48 (3H, m), 7.34-7.27 (4H, m), 3.68 (2H, s), 3.66
14 (1H, septet, J = 6.2 Hz), 3.03 (2H, q, J = 7.6 Hz), 1.33 (2H, t, J = 7.6 Hz), 1.17
15 (2H, m), 1.01 (6H, d, J = 6.2 Hz), 0.90 (2H, m).

16 (4-Bromo-3-isopropyl-phenoxy)-triisopropyl-silane (Intermediate 96)

17 To a solution of 4-bromo-3-isopropylphenol (880.0 mg, 4.09 mmols)
18 and imidazole (417.0 mg, 6.13 mmols) in 10 mL DMF was added chloro-
19 triisopropylsilane (946.0 mg, 4.90 mmols). After stirring overnight at room
20 temperature the solution was diluted with H₂O and extracted with EtOAc. The
21 combined organic layers were washed with H₂O and saturated aqueous NaCl
22 before being dried (MgSO₄) and concentrated under reduced pressure. The
23 title compound, 1.30 g (92%), was isolated by column chromatography (1-2%
24 EtOAc-hexanes) as a colorless oil.

25 ¹H NMR (CDCl₃) δ: 7.34 (1H, d, J = 8.5 Hz), 6.81 (1H, d, J = 2.9 Hz), 6.59
26 (1H, dd, J = 2.9, 8.5 Hz), 3.31 (1H, septet, J = 7.0 Hz), 1.33-1.21 (3H, m), 1.24
27 (6H, d, J = 7.0 Hz), 1.13 (18H, d, J = 7.0 Hz).

28 Ethyl 2-isopropyl-4-triisopropylsilanyloxy-benzoate (Intermediate 97)

1 To a solution of (4-bromo-3-isopropyl-phenoxy)-triisopropyl-silane
2 (**Intermediate 96**, 1.3 g, 3.8 mmols) in 15 mL Et₂O cooled to -78 °C was
3 added 4.9 mL of *tert*-butyllithium in pentane (532.0 mg, 8.3 mmols; 1.7 M).
4 After stirring for 30 minutes ethyl chloroformate (832.0 mg, 7.8 mmols) was
5 added. The resulting solution was warmed to room temperature and quenched
6 by the addition of saturated aqueous NH₄Cl. The mixture was extracted with
7 EtOAc and the combined organic layers dried (MgSO₄) concentrated under
8 reduced pressure and the residue chromatographed (4% EtOAc-hexanes) to
9 give 1.09 g (85%) of the title compound as a colorless oil.

10 ¹H NMR (CDCl₃) δ: 7.72 (1H, d, J = 8.5 Hz), 6.87 (1H, d, J = 2.3 Hz), 6.69
11 (1H, dd, J = 2.3, 8.5 Hz), 3.88 (1H, septet; J = 7.1 Hz), 4.30 (2H, q, J = 7.1
12 Hz), 1.36 (3H, t, J = 7.1 Hz), 1.31-1.17 (9H, m), 1.09 (18H).

13 [4-(1-Ethoxyvinyl)-3-isopropyl-phenoxy]-triisopropyl-silane (**Intermediate**
14 **98**)

15 Using General Procedure 1; ethyl 2-isopropyl-4-triisopropylsilanyloxy-
16 benzoate (**Intermediate 97**, 450.0 mg, 1.34 mmols) and 2.0 mL of Tebbe's
17 Reagent (398.0 mg, 1.40 mmols) afforded the title compound after column
18 chromatography (100% hexanes).

19 ¹H NMR (CDCl₃) δ: 7.11 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 2.3 Hz), 6.63
20 (1H, dd, J = 2.3, 8.2 Hz), 4.23 (1H, d, J = 1.7 Hz), 4.10 (1H, d, J = 1.7 Hz),
21 3.86 (2H, q, J = 7.0 Hz), 3.16 (1H, septet, J = 7.0 Hz), 1.35 (3H, t, J = 7.1 Hz),
22 1.28-1.19 (3H, m), 1.19 (6H, d, J = 7.0 Hz), 1.11 (18H).

23 [4-(1-Ethoxycyclopropyl)-3-isopropyl-phenoxy]-triisopropyl-silane
24 (**Intermediate 99**)

25 Using General Procedure 2; [4-(1-ethoxyvinyl)-3-isopropyl-phenoxy]-
26 triisopropyl-silane (**Intermediate 98**, 300.0 mg, 0.83 mmols), Et₂Zn (325.0
27 mg, 2.63 mmols), and CH₂I₂ (704.0 mg, 2.63 mmols) in 5.0 mL Et₂O afforded
28 270.0 mg (86%) of the title compound as a colorless oil after chromatography

1 (0.5-2.5% EtOAc - hexanes).

2 ¹H NMR (CDCl₃) δ: 7.06 (1H, d, J = 8.2 Hz), 6.81 (1H, d, J = 2.6 Hz), 6.59
3 (1H, dd, J = 2.6, 8.2 Hz), 3.76 (1H, septet, J = 7.0 Hz), 3.25 (2H, q, J = 7.0
4 Hz), 1.30-1.20 (3H, m), 1.19 (6H, d, J = 7.0 Hz), 1.15 (2H, m), 1.10 (18H),
5 1.02 (2H, t, J = 7.0 Hz), 0.82 (2H, m).

6 4-(1-Ethoxycyclopropyl)-3-isopropyl-phenol (**Intermediate 100**)

7 To a solution of [4-(1-ethoxycyclopropyl)-3-isopropyl-phenoxy]-
8 triisopropyl-silane (**Intermediate 99**, 360.0 mg, 0.96mmol) in 3 mL THF at 0
9 °C was added tetrabutylammonium fluoride (625.0 mg, 2.39 mmols, 2.4 mL of
10 a 1 M solution in THF). The solution was stirred at 0 °C for 30 minutes and
11 then quenched by the addition of H₂O. The mixture was extracted with EtOAc
12 and the combined organic layers were washed with H₂O and saturated aqueous
13 NaCl before being dried (MgSO₄) and concentrated under reduced pressure.
14 The title compound (180 mg, 86%) was isolated from the residue by column
15 chromatography (4-10% EtOAc-hexanes) as a colorless solid.

16 ¹H NMR (CDCl₃) δ: 7.13 (1H, d, J = 8.2 Hz), 6.79 (1H, d, J = 2.6 Hz), 6.57
17 (1H, dd, J = 2.6, 8.2 Hz), 5.48 (1H, s), 3.79 (1H, septet, J = 7.0 Hz), 3.32 (2H,
18 q, J = 7.0 Hz), 1.21 (6H, d, J = 7.0 Hz), 1.12 (2H, m), 1.05 (3H, t, J = 7.0 Hz),
19 0.84 (2H, m).

20 4-(1-Ethoxycyclopropyl)-3-isopropyl-phenyl 1,1,1-trifluoromethanesulfonate
21 (**Intermediate 101**)

22 A solution of 4-(1-ethoxycyclopropyl)-3-isopropyl-phenol
23 (**Intermediate 100**, 172.0 mg, 0.78 mmol) in 5 mL of CH₂Cl₂ was cooled to 0
24 °C and to it was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-
25 chloropyridine (321.0 mg, 0.82 mmol) and triethylamine (240.0 mg, 2.4
26 mmols). The resulting solution was warmed to room temperature and stirred
27 overnight. The reaction was quenched by the addition of H₂O and the mixture
28 extracted with EtOAc and the combined organic layers were washed with 10%

1 aqueous HCl, saturated aqueous NaHCO₃, H₂O, and saturated aqueous NaCl.
2 The solution was dried (MgSO₄) and concentrated under reduced pressure.
3 The title compound was isolated by column chromatography (2-4% EtOAc-
4 hexanes) as a colorless oil, 240.0 mg, 87%.
5 ¹H NMR (CDCl₃) δ: 7.31 (1H, d, J = 8.6 Hz), 7.18 (1H, d, J = 2.6 Hz), 7.00
6 (1H, dd, J = 2.6, 8.6 Hz), 3.87 (1H, septet, J = 7.0 Hz), 2.38 (2H, q, J = 7.0
7 Hz), 1.24 (6H, d, J = 7.0 Hz), 1.15 (2H, m), 1.04 (3H, t, J = 7.0 Hz), 0.86 (2H,
8 m).

9 [4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-trimethylsilane
10 **(Intermediate 102)**

11 Using General Procedure D; 4-(1-ethoxycyclopropyl)-3-isopropyl-
12 phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 101**, 240.0 mg, 0.68
13 mmol) in triethylamine (2 mL) and DMF (6 mL) was sparged with argon for 5
14 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then added
15 followed by dichlorobis-(triphenylphosphine)palladium(II) (38.0 mg, 0.05
16 mmol). The resulting reaction mixture was heated to 95 °C for 5d. The title
17 compound, 200.0 mg (99%), was isolated by chromatography (0 - 2% EtOAc -
18 hexanes) as an orange oil.

19 ¹H NMR (CDCl₃) δ: 7.43 (1H, d, J = 1.7 Hz), 7.25 (1H, dd, J = 1.7, 7.9 Hz),
20 7.16 (1H, d, J = 7.9 Hz), 3.80 (1H, septet, J = 6.8 Hz), 3.26 (2H, q, J = 7.0 Hz),
21 1.24 (6H, d, J = 6.8 Hz), 1.24-1.10 (2H, m), 1.03 (3H, t, J = 7.0 Hz), 0.87 (2H,
22 s), 0.26 (9H, s).

23 1-(1-Ethoxycyclopropyl)-4-ethynyl-2-isopropylbenzene (**Intermediate 103**)

24 Using General Procedure E; [4-(1-ethoxycyclopropyl)-3-isopropyl-
25 phenylethynyl]-trimethylsilane (**Intermediate 102**, 210.0 mg, 0.70 mmol) in
26 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72
27 mmol) and stirred overnight at ambient temperature. The crude alkyne was
28 used directly in the next reaction.

¹H NMR (CDCl₃) δ: 7.47 (1H, d, J = 1.7 Hz), 7.23 (1H, dd, J = 1.7, 7.6 Hz),
7.19 (1H, d, J = 7.6 Hz), 3.80 (1H, septet, J = 7.0 Hz), 3.27 (1H, q, J = 7.0 Hz),
3.07 (1H, s), 1.23 (6H, d, J = 7.0 Hz), 1.13 (2H, m), 1.03 (3H, t, J = 7.0 Hz),
0.85 (2H, m).

Ethyl 4-[4-(1-ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoate

(Compound 99, General Formula 2)

Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-isopropylbenzene (**Intermediate 103**, 50.0 mg, 0.22 mmol) and ethyl-4-iodobenzoate (**Reagent A**, 60.0 mg, 0.22 mmol) in triethylamine (5 mL) was treated with copper(I)iodide (14.0 mg, 0.07 mmol) and sparged with argon for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (51 mg, 0.07 mmol) was added and the reaction mixture was stirred overnight at room temperature. Column chromatography (1-2% EtOAc - hexanes) afforded 28.0 mg (34%) of the title compound.

¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.51 (1H, d, J = 1.7 Hz), 7.28 (1H, dd, J = 1.7, 7.9 Hz), 7.21 (1H, d, J = 7.9 Hz), 4.38 (2H, q, J = 7.1 Hz), 3.83 (1H, septet, J = 6.7 Hz), 3.29 (2H, q, J = 7.0 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.26 (6H, d, J = 6.7 Hz), 1.14 (2H, m), 1.04 (3H, t, J = 7.0 Hz), 0.87 (2H, m).

Methyl {4-[4-(1-ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-

acetate (Compound 100, General Formula 2)

Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-isopropylbenzene (**Intermediate 103**, 120.0 mg, 0.52 mmol) and methyl-(4-iodophenyl)-acetate (**Reagent B**, 150.0 mg, 0.52 mmol) in triethylamine (8 mL) was treated with copper(I)iodide (32.0 mg, 0.17 mmol) and sparged with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (121 mg, 0.17 mmol) was added and the reaction mixture was stirred overnight at room temperature. Column chromatography (2-5% EtOAc - hexanes) afforded

1 140.0 mg (71%) of the title compound as a pale-yellow oil.

2 ¹H NMR (CDCl₃) δ: 7.53 (3H, m), 7.31-7.23 (4H, m), 3.86 (1H, septet, J = 6.7
3 Hz), 3.73 (3H, s), 3.67 (2H, s), 3.33 (2H, q, J = 7.0 Hz), 1.30 (6H, d, J = 6.7
4 Hz), 1.15 (2H, m), 1.08 (3H, t, J = 7.0 Hz), 0.90 (2H, m).

5 4-[4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoic acid

6 **(Compound 101, General Formula 2)**

7 Using General Procedure I; A solution of ethyl 4-[4-(1-
8 ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoate (**Compound 99**,
9 28.0 mg, 0.07 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was
10 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)
11 and stirred overnight at room temperature. Work-up afforded 24 mg (92%)
12 the title compound as a pale-yellow solid.

13 ¹H NMR (d₆-acetone) δ: 8.06 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.2 Hz),
14 7.58 (1H, s), 7.33 (2H, m), 3.87 (1H, m), 2.27 (2H, q, J = 7.0 Hz), 1.26 (6H, d,
15 J = 6.7 Hz), 1.09 (2H, m), 0.99 (3H, t, J = 7.0 Hz), 0.88 (2H, m).

16 {4-[4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-acetic acid

17 **(Compound 102, General Formula 2)**

18 Using General Procedure I; a solution of methyl {4-[4-(1-
19 ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-acetate (**Compound**
20 **100**, 130.0 mg, 0.35 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL) was
21 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
22 and stirred at 50 °C for 4h. Work-up and isolation by HPLC (Partisil 10-pac,
23 10% H₂O/CH₃CN) afforded 88.0 mg (70%) of the title compound.

24 ¹H NMR (CDCl₃) δ: 7.50 (3H, m), 7.28-7.19 (4H, m), 3.82 (1H, m), 3.65 (2H,
25 s), 3.29 (2H, q, J = 7.0 Hz), 1.25 (6H, d, J = 6.7 Hz), 1.14 (2H, m), 1.04 (3H, t,
26 J = 7.0 Hz), 0.86 (2H, m).

27 4-Bromo-3-*tert*-butylphenol (**Intermediate 104**)

28 To a mixture of 3-*tert*-butyl-methoxy benzene (1.00 g, 6.09 mmols) in

1 CCl₄ (20 mL), molecular sieves, and silica gel was added *N*-bromosuccinimide
2 (1.19 g, 6.70 mmols). This mixture was stirred at 55 °C for 48h. The resulting
3 mixture was cooled to room temperature, filtered to remove the solids, and the
4 filtrate diluted with EtOAc. This solution was washed with H₂O, 10%
5 aqueous HCl, H₂O, saturated aqueous NaHCO₃ and saturated aqueous NaCl
6 before being dried (MgSO₄) and concentrated under reduced pressure.
7 Column chromatography (2.5% EtOAc-hexanes) afforded 1.15 g (78%) of a 3
8 to 1 mixture of 1-bromo-2-*tert*-butyl methoxy benzene and 1-bromo-2-
9 methoxy-4-*tert*-butyl benzene as a colorless oil.

10 A solution of the isomeric methoxy compounds in 10 mL of CH₂Cl₂
11 was cooled to 0 °C and treated with a solution (18.5 mL) of BBr₃ in CH₂Cl₂
12 (4.63 g, 18.5 mmols). After 10 minutes the solution was warmed to room
13 temperature, stirred for 1h, and then quenched with H₂O. The mixture was
14 extracted with EtOAc and the combined organic layers washed with saturated
15 aqueous NaCl, dried (MgSO₄), and concentrated under reduced pressure. The
16 title compound was isolated, 1.17 g (59%), by column chromatography (2.5-
17 5% EtOAc-hexanes).

18 ¹H NMR (CDCl₃) δ: 7.39 (1H, d, J = 8.5 Hz), 6.96 (1H, d, J = 2.9 Hz), 6.54
19 (1H, dd, J = 2.9, 8.5 Hz), 1.46 (9H, s).

20 (4-Bromo-3-*tert*-butyl-phenoxy)-triisopropyl-silane (Intermediate 105)

21 To a solution of 4-bromo-3-*tert*-butylphenol (Intermediate 104, 1.17 g,
22 5.10 mmols) and imidazole (520.0 mg, 7.65 mmols) in 10 mL DMF was added
23 chloro-triisopropylsilane (1.18 g, 6.10 mmols). After stirring overnight at
24 room temperature the solution was diluted with H₂O and extracted with
25 EtOAc. The combined organic layers were washed with H₂O and saturated
26 aqueous NaCl before being dried (MgSO₄) and concentrated under reduced
27 pressure. The title compound, 1.80 g (92%), was isolated by column
28 chromatography (0-1.5% EtOAc-hexanes) as a colorless oil.

¹H NMR (CDCl₃) δ: 7.38 (1H, d, J = 8.0 Hz), 6.97 (1H, d, J = 2.9 Hz), 6.56 (1H, dd, J = 2.9, 8.5 Hz), 1.47 (9H, s), 1.29-1.24 (3H, m), 1.09 (18H, d, J = 6.7 Hz).

Ethyl 2-*tert*-butyl-4-triisopropylsilanyloxy-benzoate (**Intermediate 106**)

To a solution of (4-bromo-3-*tert*-butyl-phenoxy)-triisopropyl-silane (**Intermediate 105**, 1.00 g, 2.60 mmols) in 15 mL Et₂O cooled to -78 °C was added 3.6 mL of *tert*-butyllithium, 1.7 M in pentane (395.0 mg, 6.2 mmols). After stirring for 30 minutes ethyl chloroformate (607.6 mg, 5.6 mmols) was added. The resulting solution was warmed to room temperature and quenched by the addition of saturated aqueous NH₄Cl. The mixture was extracted with EtOAc and the combined organic layers dried (MgSO₄) concentrated under reduced pressure. The residue was chromatographed (2-5% EtOAc-hexanes) to give 1.23 g (88%) of the title compound as a colorless oil.

¹H NMR (CDCl₃) δ: 7.24 (1H, d, J = 8.2 Hz), 6.97 (1H, d, J = 2.6 Hz), 6.69 (1H, dd, J = 2.6, 8.2 Hz), 4.33 (2H, q, J = 7.1 Hz), 1.39 (9H, s), 1.37 (3H, t, J = 7.1 Hz), 1.29-1.21 (3H, m), 1.10 (18H, d, J = 6.7 Hz).

[4-(1-Ethoxyvinyl)-3-*tert*-butyl-phenoxy]-triisopropyl-silane (**Intermediate 107**)

Using General Procedure 1; ethyl 2-*tert*-butyl-4-triisopropylsilanyloxy-benzoate (**Intermediate 106**, 1.30 g, 3.44 mmols) and 7.2 mL of Tebbe's Reagent (1.03 g, 3.61 mmols) were reacted. The reaction required 7 days at room temperature to go to completion. The standard work-up afforded 1.29 g (78%) of the title compound after column chromatography (1-2% EtOAc-hexanes).

¹H NMR (CDCl₃) δ: 7.05 (1H, d, J = 8.2 Hz), 6.94 (1H, d, J = 2.6 Hz), 6.63 (1H, dd, J = 2.6, 8.2 Hz), 4.20 (1H, d, J = 1.7 Hz), 4.08 (1H, d, J = 1.7 Hz), 3.83 (2H, q, J = 7.1 Hz), 1.37 (9H, s), 1.36 (3H, t, J = 7.1 Hz), 1.27-1.20 (3H, m), 1.10 (18H, d, J = 6.7 Hz).

1 [4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenoxy]-triisopropyl-silane

2 **(Intermediate 108)**

3 Using General Procedure 2; [4-(1-ethoxyvinyl)-3-*tert*-butyl-phenoxy]-
4 triisopropyl-silane (**Intermediate 107**, 320.0 mg, 0.85 mmols), Et₂Zn (325.0
5 mg, 2.63 mmols), and CH₂I₂ (704.0 mg, 2.63 mmols) in 5.0 mL Et₂O afforded
6 257.0 mg (66%) of the title compound as a colorless oil after chromatography
7 (1-2.5% EtOAc - hexanes).

8 ¹H NMR (CDCl₃) δ: 7.24 (1H, d, J = 8.5 Hz), 7.06 (1H, d, J = 2.6 Hz), 6.60
9 (1H, dd, J = 2.6, 8.5 Hz), 3.24 (2H, q, J = 7.1 Hz), 1.50 (9H, s), 1.29-1.21 (3H,
10 m), 1.11 (18H, d, J = 6.7 Hz), 1.04 (3H, t, J = 7.1 Hz).

11 4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenol (**Intermediate 109**)

12 To a solution of [4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenoxy]-
13 triisopropyl-silane (**Intermediate 108**, 600.0 mg, 1.54 mmol) in 3 mL THF at
14 0 °C was added tetrabutylammonium fluoride (802.8.0 mg, 3.07 mmols; 3.1
15 mL of a 1 M solution in THF). The solution was stirred at 0 °C for 30
16 minutes and then quenched by the addition of H₂O. The mixture was extracted
17 with EtOAc and the combined organic layers were washed with H₂O and
18 saturated aqueous NaCl before being dried (MgSO₄) and concentrated under
19 reduced pressure. The title compound (400 mg, 88%) was isolated from the
20 residue by column chromatography (4-10% EtOAc-hexanes) as a colorless
21 solid.

22 ¹H NMR (CDCl₃) δ: 7.29 (1H, d, J = 8.2 Hz), 7.01 (1H, d, J = 2.6 Hz), 6.57
23 (1H, dd, J = 2.6, 8.2 Hz), 3.29 (2H, q, J = 7.1 Hz), 1.59 (9H, s), 1.08-1.04 (7H,
24 m).

25 4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenyl 1,1,1-trifluoromethanesulfonate

26 **(Intermediate 110)**

27 A solution of 4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenol
28 (**Intermediate 109**, 400.0 mg, 1.71 mmol) in 10 mL of CH₂Cl₂ was cooled to

1 0 °C and to it was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-
2 chloropyridine (705.0 mg, 1.79 mmol) and triethylamine (522.0 mg, 5.1
3 mmols). The resulting solution was warmed to room temperature and stirred
4 overnight. The reaction was quenched by the addition of H₂O and the mixture
5 extracted with EtOAc and the combined organic layers were washed with 10%
6 aqueous HCl, saturated aqueous NaHCO₃, H₂O, and saturated aqueous NaCl.
7 The solution was dried (MgSO₄) and concentrated under reduced pressure.
8 The title compound was isolated by column chromatography (2-4% EtOAc-
9 hexanes) as a colorless oil, 542.0 mg (87%).
10 ¹H NMR (CDCl₃) δ: 7.48 (1H, d, J = 8.5 Hz), 7.39 (1H, d, J = 2.6 Hz), 7.01
11 (1H, dd, J = 2.6, 8.5 Hz), 3.26 (2H, q, J = 7.1 Hz), 1.52 (9H, s), 1.12 (2H, bs),
12 1.08-1.04 (5H, m).

13 [4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-trimethylsilane
14 **(Intermediate 111)**

15 Using General Procedure D; 4-(1-ethoxycyclopropyl)-3-*tert*-butyl-
16 phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 110**, 260.0 mg, 0.71
17 mmol) in triethylamine (4 mL) and DMF (6 mL) was sparged with argon for 5
18 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then added
19 followed by dichlorobis-(triphenylphosphine)palladium(II) (40.0 mg, 0.06
20 mmol). The resulting reaction mixture was heated to 95 °C for 18 hours. The
21 title compound, 215.0 mg (96%), was isolated by chromatography (0 - 2%
22 EtOAc - hexanes) as an orange oil.
23 ¹H NMR (CDCl₃) δ: 7.63 (1H, d, J = 1.7 Hz), 7.32 (1H, d, J = 7.9 Hz), 7.19
24 (1H, dd, J = 1.7, 7.9 Hz), 3.24 (2H, q, J = 7.1 Hz), 1.51 (9H, s), 1.10 (2H, bs),
25 1.06-1.01 (5H, m), 0.25 (9H, s).

26 1-(1-Ethoxycyclopropyl)-4-ethynyl-2-*tert*-butylbenzene (**Intermediate 112**)

27 Using General Procedure E; [4-(1-ethoxycyclopropyl)-3-*tert*-butyl-
28 phenylethynyl]-trimethylsilane (**Intermediate 111**, 215.0 mg, 0.69 mmol) in

1 methanol (10 mL) was treated with potassium carbonate (80.0 mg, 0.58 mmol)
2 and stirred overnight at ambient temperature. The crude alkyne, 169 mg, was
3 used directly in the next reaction.

4 ¹H NMR (CDCl₃) δ: 7.68 (1H, d, J = 1.8 Hz), 7.36 (1H, d, J = 7.9 Hz), 7.23
5 (1H, dd, J = 1.8, 7.9 Hz), 3.26 (2H, q, J = 7.1 Hz), 3.06 (1H, s), 1.51 (9H, s),
6 1.11 (2H, bs), 1.07-1.02 (5H, m).

7 Ethyl 4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoate
8 **(Compound 103, General Formula 2)**

9 Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-*tert*-
10 butylbenzene (**Intermediate 112**, 70.0 mg, 0.30 mmol) and ethyl-4-iodo
11 benzoate (**Reagent A**, 85.0 mg, 0.30 mmol) in triethylamine (5 mL) was
12 treated with copper(I)iodide (19.0 mg, 0.01 mmol) and sparged with argon for
13 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (70 mg, 0.01
14 mmol) was added and the reaction mixture was stirred overnight at room
15 temperature. Column chromatography (1-2% EtOAc - hexanes) afforded 70.0
16 mg (73%) of the title compound.

17 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.8 Hz), 7.72 (1H, d, J = 1.7 Hz), 7.59
18 (2H, d, J = 8.8 Hz), 7.40 (1H, d, J = 7.9 Hz), 7.28 (1H, dd, J = 1.7, 7.9 Hz),
19 4.39 (2H, q, J = 7.1 Hz), 3.28 (2H, q, J = 7.1 Hz), 1.55 (9H, s), 1.40 (3H, t, J =
20 7.1 Hz), 1.12 (2H, bs), 1.08-1.04 (5H, m).

21 Methyl {4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-
22 acetate **(Compound 104, General Formula 2)**

23 Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-*tert*-
24 butylbenzene (**Intermediate 112**, 95.0 mg, 0.39 mmol) and methyl-(4-
25 iodophenyl)-acetate (**Reagent B**, 108.0 mg, 0.39 mmol) in triethylamine (8
26 mL) was treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged with
27 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (91 mg,
28 0.13 mmol) was added and the reaction mixture was stirred overnight at room

1 temperature. Column chromatography (2-5% EtOAc - hexanes) afforded
2 100.0 mg (72%) of the title compound.

3 ¹H NMR (CDCl₃) δ: 7.70 (1H, d, J = 1.5 Hz), 7.50 (2H, d, J = 7.9 Hz), 7.38
4 (1H, d, J = 7.9 Hz), 7.27 (3H, m), 3.70 (3H, s), 3.64 (2H, s), 3.28 (2H, q, J =
5 7.1 Hz), 1.54 (9H, s), 1.12 (2H, bs), 1.08-1.03 (5H, m).

6 4-[4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoic acid

7 **(Compound 105, General Formula 2)**

8 Using General Procedure I; a solution of ethyl 4-[4-(1-
9 ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoate (**Compound 103**,
10 70.0 mg, 0.18 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
11 treated with NaOH (240.0 mg, 6.0 mmols, 3.0 mL of a 2N aqueous solution)
12 and stirred overnight at room temperature. Work-up afforded 40 mg (62%)
13 the title compound as a pale-yellow solid.

14 ¹H NMR (d₆-acetone) δ: 8.06 (2H, d, J = 8.7 Hz), 7.76 (1H, d, J = 1.8 Hz),
15 7.67 (2H, d, J = 8.7 Hz), 7.50 (1H, d, J = 7.9 Hz), 7.33 (1H, dd, J = 1.8, 7.9
16 Hz), 3.28 (2H, q, J = 7.3 Hz), 1.54 (9H, s), 1.13 (2H, bs), 1.10 (2H, m), 1.02
17 (3H, t, J = 7.3 Hz).

18 {4-[4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetic acid

19 **(Compound 106, General Formula 2)**

20 Using General Procedure I; a solution of methyl {4-[4-(1-
21 ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetate (**Compound**
22 **104**, 100.0 mg, 0.26 mmol) in ethanol (4 mL) and tetrahydrofuran (4 mL) was
23 treated with NaOH (240.0 mg, 6.0 mmols, 3.0 mL of a 2N aqueous solution)
24 and stirred at 50 °C for 4h. Work-up and isolation by HPLC (Partisil 10-pac,
25 10% H₂O/CH₃CN) afforded 70.0 mg (73%) of the title compound.

26 ¹H NMR (CDCl₃) δ: 7.73 (1H, d, J = 1.3 Hz), 7.53 (2H, d, J = 7.9 Hz), 7.41
27 (1H, d, J = 7.9 Hz), 7.28 (3H, m), 3.69 (2H, s), 3.31 (2H, q, J = 7.1 Hz), 1.56
28 (9H, s), 1.15 (2H, bs), 1.11-1.05 (5H, m).

1 1-(4-Bromophenyl)-cyclopropanecarbonitrile (Intermediate 113)

2 To a 50% aqueous NaOH solution (40.0 g, wt/wt) was added benzyl
3 triethylammonium chloride (1.0 g, 4.4 mmols), 4-bromobenzonitrile (19.6 g,
4 0.10 mol), and 1,2-dibromoethane (56.4 g, 0.30 mol). The mixture was stirred
5 overnight at room temperature and then diluted with 100 mL of H₂O. This
6 mixture was extracted with EtOAc and the combined extracts were washed
7 with saturated aqueous NaHS₂O₃, H₂O, and saturated aqueous NaCl before
8 being dried (MgSO₄) and concentrated under reduced pressure. Bulb-to-bulb
9 distillation afforded 18.8 g (85%) of the title compound as a colorless solid.
10 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 8.6 Hz), 7.17 (2H, d, J = 8.6 Hz), 1.75
11 (2H, dd, J = 5.2, 7.6 Hz), 1.39 (2H, dd, J = 5.2, 7.6 Hz).

12 1-(4-Bromophenyl)-cyclopropanecarboxylic acid (Intermediate 114)

13 To a solution of KOH (6.06 g, 0.11 mol) in 10 mL of H₂O was added
14 40 mL of ethylene glycol and 1-(4-bromophenyl)-cyclopropanecarbonitrile
15 (Intermediate 113, 10.0 g, 0.45 mol). This solution was heated to 135-140 °C
16 for 4h, cooled to room temperature, and then poured into a mixture of 100 mL
17 ice and 10% aqueous HCl. The resulting mixture was allowed to stand
18 overnight at 5 °C, the solid was collected by filtration and washed with H₂O.
19 The colorless solid was dried under reduced pressure to give 10.6 g (97%) of
20 the title compound.

21 ¹H NMR (CDCl₃) δ: 7.43 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 1.68
22 (2H, dd, J = 4.0, 7.1 Hz), 1.24 (2H, dd, J = 4.0, 7.1 Hz).

23 Tert-butyl [1-(4-bromophenyl)-cyclopropyl]-carbamate (Intermediate 115)

24 A solution of 1-(4-bromophenyl)-cyclopropanecarboxylic acid
25 (Intermediate 114, 2.32 g, 9.62 mmols), diphenylphosphoryl azide (2.65 g,
26 9.62 mmols), triethylamine (973.0 mg, 9.62 mmols) in 40 mL *tert*-BuOH
27 (distilled from Na^o) was heated to reflux for 17h. The solution was
28 concentrated under reduced pressure and the residue dissolved in EtOAc and

1 washed with 5% aqueous HCl, H₂O, saturated aqueous NaHCO₃, and saturated
2 aqueous NaCl before being dried over MgSO₄. Concentration of the dry
3 solution under reduced pressure and column chromatography (5-10% EtOAc -
4 hexanes) afforded 2.01 g (67%) of the title compound as a colorless solid.
5 ¹H NMR (CDCl₃) δ: 7.39 (2H, d, J = 8.3 Hz), 7.08 (2H, d, J = 8.3 Hz), 5.35
6 (1H, bs), 1.43 (9H, s), 1.26 (2H, m), 1.17 (2H, m).

7 1-(4-Bromophenyl)-cyclopropylamine (Intermediate 116)

8 To a solution of *tert*-butyl [1-(4-bromophenyl)-cyclopropyl]-carbamate
9 (**Intermediate 115**, 1.08 g, 3.40 mmols) in 20 mL MeOH and 20 mL THF was
10 added 20 mL of 3M aqueous HCl. The solution was warmed to 35 °C for 3
11 hours and then stirred for 17h at 25 °C. The reaction was quenched by
12 adjusting the pH of the solution to 12 with 3M aqueous NaOH. The mixture
13 was extracted with Et₂O and the combined organic layers were washed with
14 H₂O and saturated aqueous NaCl before being dried (MgSO₄) and
15 concentrated under reduced pressure. The title compound 613 mg (85%) was
16 used without further purification.

17 ¹H NMR (CDCl₃) δ: 7.43 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 8.3 Hz), 1.89
18 (2H, bs), 1.07 (2H, m), 0.95 (2H, m).

19 N-[1-(4-bromophenyl)-cyclopropyl]-propionamide (Intermediate 117)

20 To a solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate**
21 **116**, 84 mg, 0.4 mmol) in 4 mL CH₂Cl₂ at room temperature was added
22 propionyl chloride (43.0 mg, 0.47 mmol) and pyridine (56.0 mg, 0.71 mmol).
23 After stirring 17 hours at room temperature the reaction was quenched by the
24 addition of H₂O and extracted with EtOAc. The combined extracts were
25 washed with 10% aqueous HCl, saturated aqueous NaHCO₃, and saturated
26 aqueous NaCl before being dried (MgSO₄) and concentrated under reduced
27 pressure. The title compound 85.0 mg (67%), was isolated by column
28 chromatography (20-50% EtOAc-hexanes) as a colorless solid.

1 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 8.5 Hz), 7.09 (2H, d, J = 8.5 Hz), 6.40
2 (1H, s), 2.19 (2H, q, J = 7.2 Hz), 1.18-1.24 (4H, m), 1.12 (3H, t, J = 7.2 Hz).

3 [1-(4-Bromophenyl)-cyclopropyl]-propylamine (Intermediate 118)

4 To a solution of *N*-[1-(4-bromophenyl)-cyclopropyl]-propionamide
5 (**Intermediate 117**, 85.0 mg, 0.32 mmol) in THF (5 mL) at 0 °C was added
6 BH₃-Me₂S (48.0 mg, 0.63 mmol; 0.31 mL of a 2M solution in THF). The
7 solution was heated to 55 °C for 17 hours, cooled to room temperature,
8 saturated aqueous NaHCO₃ was added and the resulting mixture was stirred
9 for 2 hours. This mixture was extracted with EtOAc and the combined organic
10 layers were washed with H₂O and saturated aqueous NaCl before being dried
11 (MgSO₄) and concentrated under reduced pressure. The title compound was
12 isolated by column chromatography (10-30% EtOAc-hexanes).

13 ¹H NMR (CDCl₃) δ: 7.42 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.5 Hz), 2.46
14 (2H, t, J = 7.3 Hz), 1.40 (2H, m), 0.98 (2H, m), 0.86 (5H, m).

15 Propyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine
16 (**Intermediate 119**)

17 Using General Procedure D; [1-(4-bromophenyl)-cyclopropyl]-
18 propylamine (**Intermediate 118**, 100.0 mg, 0.39 mmol) in triethylamine (8
19 mL) was treated with copper(I)iodide (13.0 mg, 0.06 mmol) and then sparged
20 with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was
21 then added followed by dichlorobis(triphenylphosphine)palladium(II) (48.0
22 mg, 0.06 mmol). The resulting reaction mixture was heated to 70 °C for
23 5 days. The title compound (80.0 mg, 75%) was isolated by chromatography
24 (0 - 10% EtOAc - hexanes) as an orange oil.

25 ¹H NMR (CDCl₃) δ: 7.41 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 2.45
26 (2H, t, J = 7.3 Hz), 1.39 (2H, m), 0.98 (2H, m), 0.87 (2H, m), 0.84 (3H, t, J =
27 7.3 Hz), 0.24 (9H, s).

28 [1-(4-Ethynylphenyl)-cyclopropyl]-propylamine (Intermediate 120)

1 Using General Procedure E; propyl-[1-(4-trimethylsilylphenyl)-
2 phenyl]-cyclopropyl]-amine (**Intermediate 119**, 80.0 mg, 0.30 mmols) in
3 methanol (8 mL) was treated with potassium carbonate (80.0 mg, 0.59 mmol)
4 and stirred overnight at ambient temperature. The crude alkyne (58 mg,
5 100%) was used directly in the next reaction.

6 ¹H NMR (CDCl₃) δ: 7.44 (2H, d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz), 3.05
7 (1H, s), 2.46 (2H, t, J = 7.3 Hz), 1.41 (2H, m), 1.00 (2H, m), 0.90 (2H, m),
8 0.86 (3H, t, J = 7.3 Hz).

9 Ethyl 4-[4-(1-propylamino-cyclopropyl)-phenylethynyl]-benzoate
10 (**Compound 107**, General Formula 2)

11 Using General Procedure F; [1-(4-ethynylphenyl)-cyclopropyl]-
12 propylamine (**Intermediate 120**, 38.0 mg, 0.19 mmol) and ethyl-4-iodo
13 benzoate (**Reagent A**, 58.0 mg, 0.21 mmol) in triethyl amine (6 mL) was
14 treated with copper(I)iodide (8.0 mg, 0.04 mmol) and sparged with argon for 5
15 minutes. Dichlorobis(triphenylphosphine)palladium(II) (27 mg, 0.04 mmol)
16 was added and the reaction mixture was stirred overnight at room temperature.
17 Column chromatography (5-15% EtOAc - hexanes) afforded 40.0 mg (61%)
18 of the title compound as an orange oil.

19 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.49
20 (2H, d, J = 8.5 Hz), 7.28 (2H, d, J = 8.5 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.49
21 (2H, t, J = 7.3 Hz), 1.46 (2H, m), 1.41 (3H, t, J = 7.1 Hz), 1.01 (2H, m), 0.89
22 (2H, m), 0.87 (3H, t, J = 7.3 Hz).

23 4-[4-(1-Propylamino-cyclopropyl)-phenylethynyl]-benzoic acid (**Compound**
24 **108**, General Formula 2)

25 Using General Procedure I; a solution of ethyl 4-[4-(1-propylamino-
26 cyclopropyl)-phenylethynyl]-benzoate (**Compound 107**, 40.0 mg, 0.12 mmol)
27 in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with NaOH (160.0
28 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and stirred overnight at

1 room temperature. Work-up afforded 25.0 mg (69%) of the title compound as
2 a solid.

3 ^1H NMR (d_6 -DMSO) δ : 7.97 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz), 7.50
4 (2H, d, J = 8.5 Hz), 7.36 (2H, d, J = 8.5 Hz), 2.39 (2H, t, J = 7.3 Hz), 1.37 (2H,
5 m), 1.00 (2H, m), 0.93 (2H, m), 0.84 (3H, t, J = 7.3 Hz).

6 [1-(4-Bromophenyl)-cyclopropyl]-dipropylamine (Intermediate 121)

7 To a solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate**
8 **116**) in CH_3CN / HOAc (5 mL, 9:1, v/v) and THF 3 mL at 0 °C was added
9 propionaldehyde (277.0 mg, 4.95 mmols) and NaCNBH_3 (153.0 mg, 2.47
10 mmols). The reaction was warmed to room temperature and after 5 hours
11 quenched with H_2O . The pH of the solution was adjusted to 8-9 using aqueous
12 NaOH and extracted with EtOAc. The combined extracts were washed with
13 H_2O and saturated aqueous NaCl, dried (MgSO_4) and concentrated under
14 reduced pressure. The title compound, 190.0 mg (56%), was isolated by
15 column chromatography (2-5% EtOAc-hexanes).

16 ^1H NMR (CDCl_3) δ : 7.42 (2H, d, J = 8.3 Hz), 7.18 (2H, d, J = 8.3 Hz), 2.39
17 (4H, t, J = 7.3 Hz), 1.62-1.40 (4H, m), 0.96 (2H, m), 0.86 (6H, t, J = 7.3 Hz),
18 0.80 (2H, m).

19 Dipropyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine
20 (**Intermediate 122**)

21 Using General Procedure D; [1-(4-bromophenyl)-cyclopropyl]-
22 dipropylamine (**Intermediate 121**, 150.0 mg, 0.50 mmol) in triethylamine (5
23 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then sparged
24 with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was
25 then added followed by dichlorobis(triphenylphosphine)palladium(II) (35.0
26 mg, 0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d.
27 The title compound was isolated by chromatography (0 - 3% EtOAc -
28 hexanes).

¹H NMR (CDCl₃) δ: 7.35 (2H, d, J = 8.3 Hz), 7.24 (2H, d, J = 8.3 Hz), 2.39 (4H, t, J = 7.3 Hz), 1.55-1.42 (4H, m), 0.96 (2H, m), 0.88-0.79 (8H, m), 0.25 (9H, s).

[1-(4-Ethynylphenyl)-cyclopropyl]-dipropylamine (Intermediate 123)

Using General Procedure E; dipropyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine (**Intermediate 122**, 45.0 mg, 0.14 mmols) in methanol (5 mL) was treated with potassium carbonate (50.0 mg, 0.37 mmol) and stirred overnight at ambient temperature. The crude alkyne (34 mg, 100%) was used directly in the next reaction.

¹H NMR (CDCl₃) δ: 7.42 (2H, d, J = 8.3 Hz), 7.28 (2H, d, J = 8.3 Hz), 2.40 (4H, t, J = 7.3 Hz), 1.53-1.40 (4H, m), 0.96 (2H, m), 0.90-0.79 (8H, m).

Ethyl 4-[4-(1-dipropylamino-cyclopropyl)-phenylethynyl]-benzoate
(**Compound 109, General Formula 2**)

Using General Procedure F; [1-(4-ethynylphenyl)-cyclopropyl]-dipropylamine (**Intermediate 123**, 34.0 mg, 0.16 mmol) and ethyl-4-iodobenzoate (**Reagent A**, 59.0 mg, 0.21 mmol) in triethyl amine (6 mL) was treated with copper(I)iodide (13.0 mg, 0.07 mmol) and sparged with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (49 mg, 0.07 mmol) was added and the reaction mixture was stirred overnight at room temperature. Column chromatography (2-4% EtOAc - hexanes) afforded the title compound as a yellow oil.

¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.49 (2H, d, J = 8.2 Hz), 7.30 (2H, d, J = 8.2 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.43 (4H, t, J = 7.3 Hz), 1.52-1.42 (4H, m), 1.41 (3H, t, J = 7.1 Hz), 0.99 (2H, m), 0.88-0.83 (8H, m).

4-[4-(1-Dipropylamino-cyclopropyl)-phenylethynyl]-benzoic acid
(**Compound 110, General Formula 2**)

Using General Procedure I; a solution of ethyl 4-[4-(1-dipropylamino-

1 cyclopropyl)-phenylethynyl]-benzoate (**Compound 109**, 51.0 mg, 0.13 mmol)
2 in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with NaOH (80.0
3 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred overnight at
4 room temperature. Work-up afforded 32.0 mg (70%) of the title compound as
5 a colorless solid.

6 ¹H NMR (d₆-DMSO) δ: 7.98 (2H, d, J = 8.3 Hz), 7.67 (6H, m), 3.05-2.89 (4H,
7 m), 1.98 (2H, m), 1.72 (4H, m), 1.23 (2H, m), 0.88 (6H, t, J = 7.3 Hz).

8 Benzyl-[1-(4-bromophenyl)-cyclopropyl]-amine (**Intermediate 124**) and
9 Dibenzyl-[1-(4-bromophenyl)-cyclopropyl]-amine (**Intermediate 125**)

10 A solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate 116**,
11 244.0 mg, 1.15 mmols) and benzyl bromide (255.0 mg, 1.50 mmols) in 4 mL
12 DMF was stirred at 85 °C for 6 hours, cooled to room temperature and stirred
13 overnight. The solution was diluted with H₂O and the pH adjusted to 8-9 with
14 aqueous NaOH. The solution was extracted with EtOAc and the combined
15 organic layers were washed with H₂O and saturated aqueous NaCl, dried
16 (MgSO₄) and concentrated under reduced pressure. Column chromatography
17 (5-10% EtOAc-Hexanes) afforded 110 mg (32%) of the *N*-benzyl amine.

18 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 8.4 Hz), 7.30-7.23 (7H, m), 3.68 (2H, s),
19 1.07 (2H, m), 0.93 (2H, m); and 100 mg (22%) of the *N,N*-dibenzyl amine, ¹H
20 NMR (CDCl₃) δ: 7.55 (2H, d, J = 8.3 Hz), 7.40-7.19 (12H, m), 3.61 (4H, s),
21 0.87 (2H, m), 0.71 (2H, m).

22 Benzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine
23 (**Intermediate 126**)

24 Using General Procedure D; benzyl-[1-(4-bromophenyl)-cyclopropyl]-
25 amine (**Intermediate 124**, 110.0 mg, 0.36 mmol) in triethylamine (8 mL) was
26 treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then sparged with
27 argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was then
28 added followed by dichlorobis(triphenylphosphine)palladium(II) (38.0 mg,

0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d. The title compound 85 mg (74%) was isolated by chromatography (1 - 10% EtOAc - hexanes).

¹H NMR (CDCl₃) δ: 7.46 (2H, d, J = 8.3 Hz), 7.31-7.22 (7H, m), 3.67 (2H, s), 1.06 (2H, m), 0.94 (2H, m), 0.26 (9H, s).

Benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (Intermediate 127)

Using General Procedure E; benzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine (**Intermediate 126**, 85.0 mg, 0.27 mmol) in methanol (5 mL) was treated with potassium carbonate (50.0 mg, 0.37 mmol) and stirred overnight at ambient temperature. The crude alkyne (65 mg, 100%) was used directly in the next reaction.

¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 7.9 Hz), 7.32 (2H, d, J = 7.9 Hz), 7.23 (5H, m), 3.68 (2H, s), 3.08 (1H, s), 1.07 (2H, m), 0.95 (2H, m).

Ethyl 4-[4-(1-benzylamino-cyclopropyl)-phenylethynyl]-benzoate (Compound 111, General Formula 2)

Using General Procedure F; benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (**Intermediate 127**, 65.0 mg, 0.27 mmol) and ethyl-4-iodo benzoate (**Reagent A**, 68.0 mg, 0.27 mmol) in triethyl amine (8 mL) was treated with copper(I)iodide (16.0 mg, 0.08 mmol) and sparged with argon for 5 minutes. Dichlorobis (triphenylphosphine)palladium(II) (58 mg, 0.08 mmol) was added and the reaction mixture was stirred overnight at room temperature. Column chromatography (2-5% EtOAc - hexanes) afforded 90 mg (90%) of the title compound as an orange solid.

¹H NMR (CDCl₃) δ: 8.05 (2H, d, J = 8.3 Hz), 7.61 (2H, d, J = 8.3 Hz), 7.55 (2H, d, J = 8.1 Hz), 7.43 (2H, d, J = 8.1 Hz), 7.32-7.22 (5H, m), 4.40 (2H, q, J = 7.1 Hz), 3.72 (2H, s), 1.42 (2H, t, J = 7.1 Hz), 1.01 (2H, m), 0.99 (2H, m).

4-[4-(1-Benzylamino-cyclopropyl)-phenylethynyl]-benzoic acid (Compound 112, General Formula 2)

1 Using General Procedure I; a solution of ethyl 4-[4-(1-benzylamino-
2 cyclopropyl)-phenylethynyl]-benzoate (**Compound 111**, 75.0 mg, 0.19 mmol)
3 in ethanol (4 mL) and tetrahydrofuran (4 mL) was treated with NaOH (80.0
4 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred overnight at
5 room temperature. Work-up afforded 35.0 mg (50%) of the title compound as
6 a colorless solid.

7 ¹H NMR (CD₃OD) δ: 7.93 (2H, d, J = 8.3 Hz), 7.61-7.51 (6H, m), 7.32-7.23
8 (5H, m), 3.98 (2H, s), 1.33(2H, m), 1.19 (2H, m).

9 Dibenzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine
10 (**Intermediate 128**)

11 Using General Procedure D; dibenzyl-[1-(4-bromophenyl)-
12 cyclopropyl]-amine (**Intermediate 125**, 45.0 mg, 0.11 mmol) in triethylamine
13 (8 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then
14 sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.35 g, 3.6
15 mmols) was then added followed by
16 dichlorobis(triphenylphosphine)palladium(II) (35.0 mg, 0.05 mmol). The
17 resulting reaction mixture was heated to 70 °C for 5d. The title compound 40
18 mg (88%) was isolated by chromatography (hexanes).

19 ¹H NMR (CDCl₃) δ: 7.52 (2H, d, J = 8.3 Hz), 7.36-7.24 (12H, m), 3.60 (4H, s),
20 0.87 (2H, m), 0.67 (2H, m), 0.29 (9H, s).

21 Dibenzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (**Intermediate 129**)

22 Using General Procedure E; dibenzyl-[1-(4-trimethylsilanylethynyl-
23 phenyl)-cyclopropyl]-amine (**Intermediate 128**, 100.0 mg, 0.26 mmol) in
24 methanol (5 mL) was treated with potassium carbonate (60.0 mg, 0.44 mmol)
25 and stirred overnight at ambient temperature. The crude alkyne (80 mg, 99%)
26 was used directly in the next reaction.

27 ¹H NMR (CDCl₃) δ: 7.53 (2H, d, J = 7.9 Hz), 7.36 (2H, d, J = 7.9 Hz), 7.28-
28 7.25 (10H, m), 3.62 (4H, s), 3.11 (1H, s), 0.88 (2H, m), 0.68 (2H, m).

1 Ethyl 4-[4-(1-dibenzylamino-cyclopropyl)-phenylethynyl]-benzoate

2 **(Compound 113, General Formula 2)**

3 Using General Procedure F; dibenzyl-[1-(4-ethynylphenyl)-
4 cyclopropyl]-amine (**Intermediate 129**, 40.0 mg, 0.12 mmol) and ethyl-4-iodo
5 benzoate (**Reagent A**, 60.0 mg, 0.22 mmol) in triethylamine (5 mL) was
6 treated with copper(I)iodide (8.0 mg, 0.04 mmol) and sparged with argon for 5
7 minutes. Dichlorobis (triphenylphosphine)palladium(II) (27 mg, 0.04 mmol)
8 was added and the reaction mixture was stirred overnight at room temperature.
9 Column chromatography (2-5% EtOAc - hexanes) afforded the title compound
10 as an oil.

11 ¹H NMR (CDCl₃) δ: 8.04 (2H, d, J = 8.5 Hz), 7.79 (4H, m), 7.42 (2H, d, J =
12 7.9 Hz), 7.29-7.17 (10H, m), 4.40 (2H, q, J = 7.1 Hz), 3.63 (4H, s), 1.42 (3H, t,
13 J = 7.1 Hz), 0.88 (2H, m), 0.73 (2H, m).

14 4-[4-(1-Dibenzylamino-cyclopropyl)-phenylethynyl]-benzoic acid

15 **(Compound 114, Formula 2)**

16 Using General Procedure I; a solution of ethyl 4-[4-(1-dibenzylamino-
17 cyclopropyl)-phenylethynyl]-benzoate (**Compound 113**, 48.0 mg, 0.10 mmol)
18 in ethanol (2 mL) and tetrahydrofuran (2 mL) was treated with NaOH (80.0
19 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred overnight at
20 room temperature. Work-up afforded 42.0 mg (93%) of the title compound as
21 a colorless solid.

22 ¹H NMR (d₆-DMSO) δ: 7.98 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz), 7.64
23 (2H, d, J = 7.9 Hz), 7.47 (2H, d, J = 7.9 Hz), 7.28-7.20 (10H, m), 3.57 (4H, s),
24 0.84 (2H, m), 0.69 (2H, m).

25 Benzyl-[1-(4-bromophenyl)-cyclopropyl]-methylamine (**Intermediate 130**)

26 To a solution of benzyl-[1-(4-bromophenyl)-cyclopropyl]-amine
27 (**Intermediate 124**, 100.0 mg, 0.33 mmol) in 5 mL of acetone was added
28 K₂CO₃ (91 mg, 0.66 mmol) and iodomethane (2.28 g, 16.1 mmols). The

1 resulting mixture was stirred at 25 °C for 20 hours, diluted with Et₂O, and
2 washed with H₂O and saturated aqueous NaCl. The solution was dried
3 (MgSO₄) and concentrated under reduced pressure to give 90 mg (86%) of the
4 title compound.

5 ¹H NMR (CDCl₃) δ: 7.47 (2H, d, J = 8.5 Hz), 7.29-7.18 (7H, m), 3.53 (2H, s),
6 2.07 (3H, s), 1.07 (2H, m), 0.86 (2H, m).

7 Benzyl-[1-(4-trimethylsilanylethynyl)-phenyl]-cyclopropyl]-methylamine
8 **(Intermediate 131)**

9 Using General Procedure D; benzyl-[1-(4-bromophenyl)-cyclopropyl]-
10 methylamine (**Intermediate 130**, 90.0 mg, 0.28 mmol) in triethylamine (8
11 mL) was treated with copper(I)iodide (6.0 mg, 0.03 mmol) and then sparged
12 with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was
13 then added followed by dichlorobis(triphenylphosphine)palladium(II) (20.0
14 mg, 0.03 mmol). The resulting reaction mixture was heated to 70 °C for 5
15 days. The title compound 80 mg (84%) was isolated by chromatography (0-
16 2% EtOAc-hexanes).

17 ¹H NMR (CDCl₃) δ: 7.46 (2H, d, J = 8.2 Hz), 7.32-7.18 (7H, m), 3.52 (2H, s),
18 2.06 (3H, s), 1.06 (2H, m), 0.87(2H, m), 0.26 (9H, s).

19 Benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-methylamine (**Intermediate 132**)

20 Using General Procedure E; benzyl-[1-(4-trimethylsilanylethynyl-
21 phenyl)-cyclopropyl]-methylamine (**Intermediate 131**, 80.0 mg, 0.24 mmol)
22 in methanol (5 mL) was treated with potassium carbonate (80.0 mg, 0.59
23 mmol) and stirred overnight at ambient temperature. The crude alkyne (60
24 mg, 99%) was used directly in the next reaction.

25 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.2 Hz), 7.33-7.21 (7H, m), 3.55 (2H, s),
26 3.08 (1H, s), 2.08 (3H, s), 1.07 (2H, m), 0.89 (2H, m).

27 Ethyl 4-{4-[1-(benzyl-methylamino)-cyclopropyl]-phenylethynyl}-benzoate
28 **(Compound 115, General Formula 2)**

1 Using General Procedure F; benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-
2 methylamine (**Intermediate 132**, 70.0 mg, 0.28 mmol) and ethyl-4-iodo
3 benzoate (**Reagent A**, 77.0 mg, 0.28 mmol) in triethylamine (5 mL) was
4 treated with copper(I)iodide (18.0 mg, 0.10 mmol) and sparged with argon for
5 5 minutes. Dichlorobis (triphenylphosphine)palladium(II) (65 mg, 0.10 mmol)
6 was added and the reaction mixture was stirred overnight at room temperature.
7 Column chromatography (2-5% EtOAc - hexanes) afforded 86 mg (75%) of
8 the title compound as an oil.

9 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.53
10 (2H, d, J = 8.2 Hz), 7.36 (2H, d, J = 8.2 Hz), 7.25 (5H, m), 4.39 (2H, q, J = 7.1
11 Hz), 3.57 (2H, s), 2.10 (3H, s), 1.41 (3H, t, J = 7.1 Hz), 1.10 (2H, m), 0.92
12 (2H, m).

13 4-[4-(1-Benzylmethylamino-cyclopropyl)-phenylethynyl]-benzoic acid
14 (**Compound 116, General Formula 2**)

15 Using General Procedure I; a solution of ethyl 4-{4-[1-(benzyl-
16 methylamino)-cyclopropyl]-phenylethynyl}-benzoate (**Compound 115**, 65.0
17 mg, 0.16 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated
18 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and
19 stirred overnight at room temperature. Work-up afforded 45.0 mg (75%) of
20 the title compound as a solid.

21 ¹H NMR (d₆-DMSO) δ: 7.96 (2H, d, J = 8.3 Hz), 7.66 (2H, d, J = 8.3 Hz), 7.58
22 (2H, d, J = 8.2 Hz), 7.42 (2H, d, J = 8.2 Hz), 7.29-7.18 (5H, m), 3.52 (2H, s),
23 2.00 (3H, s), 1.02 (2H, m), 0.87 (2H, m).

24 (4-Bromo-2-methyl-phenyl)-methanol (**Intermediate 133**)

25 A solution of methyl 4-bromo-2-methyl-benzoate (1.05 g, 4.58 mmols)
26 in 10 mL of Et₂O was cooled to 0 °C and treated with LiAlH₄ (177.0 mg, 4.58
27 mmols), stirred for 3 hours, and then carefully quenched with H₂O. The
28 mixture was extracted with Et₂O and the combined organic layers were

1 washed with H₂O and saturated aqueous NaCl, dried (MgSO₄), and
2 concentrated under reduced pressure. The title compound, 830.0 mg (90%),
3 was isolated by column chromatography (10-30% EtOAc-hexanes) as a
4 colorless oil.

5 ¹H NMR (CDCl₃) δ: 7.30 (2H, m), 7.18 (1H, d, J = 8.8 Hz), 4.57 (2H, d, J =
6 5.5 Hz), 2.27 (3H, s), 2.13 (1H, t, J = 5.5 Hz).

7 (4-Bromo-2-methyl-benzyloxy)-trimethylsilane (**Intermediate 134**)

8 To a solution of (4-bromo-2-methyl-phenyl)-methanol (**Intermediate**
9 **133**, 500.0 mg, 2.48 mmols), in 10 mL THF was added triethylamine (374.0
10 mg, 3.70 mmols) and chlorotrimethylsilane (297.0 mg, 2.70 mmols). The
11 resulting solution was stirred for 17 hours at 25 °C and then treated with H₂O
12 and extracted with Et₂O. The combined organic layers were washed with H₂O,
13 10% aqueous HCl, saturated NaHCO₃, and saturated NaCl before being dried
14 (MgSO₄) and concentrated under reduced pressure. The title compound, 550.0
15 mg (81%), was isolated by column chromatography (5% EtOAc-hexanes) as a
16 colorless oil.

17 ¹H NMR (CDCl₃) δ: 7.35-7.28 (3H, m), 4.64 (2H, s), 2.29 (3H, s), 0.20 (9H,
18 s).

19 2-Methyl-4-trimethylsilyl-ethynyl-1-trimethylsilyloxymethyl-benzene
20 (**Intermediate 135**)

21 Using General Procedure D; (4-bromo-2-methyl-benzyloxy)-
22 trimethylsilane (**Intermediate 134**, 550.0 mg, 2.01 mmol) in triethylamine (8
23 mL) was treated with copper(I)iodide (38.0 mg, 0.20 mmol) and then sparged
24 with argon for 5 minutes. Trimethylsilyl acetylene (1.05 g, 10.6 mmols) was
25 then added followed by dichlorobis(triphenylphosphine)palladium(II) (142.0
26 mg, 0.20 mmol). The resulting reaction mixture was heated to 70 °C for 5
27 days. The title compound (380.0 mg, 65%) was isolated by chromatography
28 (0 - 2% EtOAc - hexanes) as an orange oil.

1 ¹H NMR (CDCl₃) δ: 7.31 (3H, m), 4.64 (2H, s), 2.24 (3H, s), 0.24 (9H, s), 0.15
2 (9H, s).

3 (4-Ethynyl-2-methyl-phenyl)-methanol (Intermediate 136)

4 Using General Procedure E; 2-methyl-4-trimethylsilanylethynyl-1-
5 trimethylsilananyloxymethyl-benzene (**Intermediate 135**, 380.0 mg, 1.30
6 mmols) in methanol (10 mL) was treated with potassium carbonate (180.0 mg,
7 1.3 mmol) and stirred overnight at ambient temperature. The crude alkyne
8 was purified by column chromatography (5-20% EtOAc-hexanes) to give
9 100.0 mg (34%) of the title compound.

10 ¹H NMR (CDCl₃) δ: 7.06 (3H, m), 4.42 (2H, d, J = 5.2 Hz), 2.81 (1H, s), 2.05
11 (3H, s), 1.59 (1H, t, J = 5.2 Hz).

12 Ethyl 4-(4-hydroxymethyl-3-methyl-phenylethynyl)-benzoate (Compound
13 **117, General Formula 6)**

14 Using General Procedure F; (4-ethynyl-2-methyl-phenyl)-methanol
15 (**Intermediate 136**, 100.0 mg, 0.44 mmol) and ethyl-4-iodo benzoate
16 (**Reagent A**, 125.0 mg, 0.45 mmol) in triethyl amine (4 mL) was treated with
17 copper(I)iodide (29 mg, 0.15 mmol) and sparged with argon for 5 minutes.
18 Dichlorobis(triphenylphosphine)palladium(II) (102 mg, 0.15 mmol) was added
19 and the reaction mixture was stirred overnight at room temperature. Column
20 chromatography (20-40% EtOAc - hexanes) afforded 130.0 mg (99%) of the
21 title compound as an orange solid.

22 ¹H NMR (CDCl₃) δ: 7.98 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.36
23 (3H, m), 4.65 (2H, s), 4.36 (2H, q, J = 7.1 Hz), 2.40 (1H, s), 2.30 (3H, s), 1.39
24 (3H, t, J = 7.1 Hz).

25 Ethyl 4-(4-bromomethyl-3-methyl-phenylethynyl)-benzoate (Intermediate
26 **137)**

27 A solution of ethyl 4-(4-hydroxymethyl-3-methyl-phenylethynyl)-
28 benzoate (**Compound 117**, 130.0 mg, 0.44 mmol) and triphenylphosphine

1 (150.0 mg, 0.57 mmol) in 5 mL CH₂Cl₂ was cooled to 0 °C and *N*-
2 bromosuccinimide (101.0 mg, 0.57 mmol) was added in 5 portions over 20
3 minutes. The solution was warmed to 25 °C and stirred for 17 hours. The
4 reaction was quenched by the addition of dilute aqueous NaHCO₃. The
5 resulting mixture was extracted with Et₂O and the combined organic layers
6 were washed with H₂O and saturated aqueous NaCl before being dried
7 (Na₂SO₄) and concentrated under reduced pressure. The title compound, 120.0
8 mg (76%), was isolated by column chromatography (2-5% EtOAc-hexanes) as
9 a colorless solid.

10 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.1 Hz), 7.56 (2H, d, J = 8.1 Hz), 7.32
11 (3H, m), 4.48 (2H, s), 4.38 (2H, q, J = 7.1 Hz), 2.40 (3H, s), 1.39 (3H, t, J =
12 7.1 Hz).

13 Ethyl 4-(4-imidazol-1-yl-methyl-3-methyl-phenylethynyl)-benzoate
14 **(Compound 118, General Formula 6)**

15 A solution of imidazole (30.0 mg, 0.44 mmol) in 2 mL DMF was
16 treated with NaH (11.0 mg, 0.44 mmol) and heated to 90 °C. After 1 h a
17 solution of ethyl 4-(4-bromomethyl-3-methyl-phenylethynyl)-benzoate
18 (**Intermediate 137**, 120.0 mg, 0.34 mmol) in 2 mL DMF was added and
19 stirring at 90 °C continued for 1 hour. The solution was cooled to room
20 temperature and concentrated under reduced pressure. The title compound,
21 90.0 mg (71%) was isolated by column chromatography (20-100% EtOAc-
22 hexanes) as a colorless solid.

23 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.51
24 (1H, s), 7.40 (1H, s), 7.36 (1H, dd, J = 1.2, 7.9 Hz), 7.10 (1H, s), 6.93 (1H, d, J
25 = 7.9 Hz), 6.88 (1H, t, J = 1.7 Hz), 5.12 (2H, s), 4.38 (2H, q, J = 7.1 Hz), 2.27
26 (3H, s), 1.40 (3H, t, J = 7.1 Hz).

27 4-(4-Imidazol-1-yl-methyl-3-methyl-phenylethynyl)-benzoic acid
28 **(Compound 119, General Formula 6)**

1 Using General Procedure I; a solution of ethyl 4-(4-imidazol-1-
2 ylmethyl-3-methyl-phenylethynyl)-benzoate (**Compound 118**, 82.0 mg, 0.24
3 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with NaOH
4 (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred overnight
5 at room temperature. Work-up afforded 51.0 mg (68%) of the title compound
6 as a solid.

7 ¹H NMR (d₆-DMSO) δ: 9.20 (1H, s), 7.97 (2H, d, J = 8.2 Hz), 7.73 (2H, m),
8 7.65 (2H, d, J = 8.2 Hz), 7.52 (1H, s), 7.46 (1H, d, J = 7.9 Hz), 7.13 (1H, d, J =
9 7.9 Hz), 5.50 (2H, s), 2.32 (3H, s).

10 4-Bromo-1-bromomethyl-2-methyl-benzene (**Intermediate 138**)

11 A solution of (4-bromo-2-methyl-phenyl)-methanol (**Intermediate 133**,
12 319.0 mg, 1.58 mmol) and triphenylphosphine (466.0 mg, 1.74 mmol) in 5 mL
13 CH₂Cl₂ was cooled to 0 °C and *N*-bromosuccinimide (309.0 mg, 1.74 mmol)
14 was added in 5 portions over 20 minutes. The solution was warmed to 25 °C
15 and stirred for 17 hours. The reaction was quenched by the addition of dilute
16 aqueous NaHCO₃. The resulting mixture was extracted with Et₂O and the
17 combined organic layers were washed with H₂O and saturated aqueous NaCl
18 before being dried (Na₂SO₄) and concentrated under reduced pressure. The
19 title compound, 350.0 mg (84%), was isolated by column chromatography (2-
20 3% EtOAc-hexanes) as a colorless oil.

21 ¹H NMR (CDCl₃) δ: 7.32 (1H, d, J = 2.0 Hz), 7.29 (1H, dd, J = 2.0, 7.9 Hz),
22 7.15 (1H, d, J = 7.9 Hz), 4.43 (2H, s), 2.37 (3H, s).

23 1-(4-Bromo-2-methyl-benzyl)-1*H*-imidazole (**Intermediate 139**)

24 A solution of imidazole (58.0 mg, 0.86 mmol) in 3 mL DMF was
25 treated with NaH (20.0 mg, 0.86 mmol) and heated to 90 °C. After 1h a
26 solution of 4-bromo-1-bromomethyl-2-methyl-benzene (**Intermediate 138**,
27 190.0 mg, 0.72 mmol) in 3 mL DMF was added and stirring at 90 °C
28 continued for 1 hour. The solution was cooled to room temperature and

1 concentrated under reduced pressure. The title compound, 160.0 mg (88%)
2 was isolated by column chromatography (5% MeOH-EtOAc) as a colorless
3 solid.
4 ¹H NMR (CDCl₃) δ: 7.46 (1H, s), 7.34 (1H, dd, J = 1.8 Hz), 7.30 (1H, dd, J =
5 1.8, 8.2 Hz), 7.08 (1H, t, J = 1.2 Hz), 6.83 (1H, t, J = 1.2 Hz), 6.80 (1H, d, J =
6 8.2 Hz), 5.03 (2H, s), 2.23 (3H, s).

7 1-(2-Methyl-4-trimethylsilanylethynyl-benzyl)-1H-imidazole (**Intermediate**
8 **140**)

9 Using General Procedure D; 1-(4-bromo-2-methyl-benzyl)-1H-
10 imidazole (**Intermediate 139**, 160.0 mg, 0.64 mmol) in triethylamine (8 mL)
11 was treated with copper(I)iodide (12.0 mg, 0.07 mmol) and then sparged with
12 argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 0.71 mmols) was then
13 added followed by dichlorobis(triphenylphosphine)palladium(II) (45.0 mg,
14 0.07 mmol). The resulting reaction mixture was heated to 70 °C for 5 days.
15 The title compound (140.0 mg, 82%) was isolated by chromatography (5%
16 MeOH-EtOAc) as an orange oil.
17 ¹H NMR (CDCl₃) δ: 7.53 (1H, s), 7.38 (1H, s), 7.34 (1H, d, J = 8.0 Hz), 7.15
18 (1H, s), 6.94 (1H, s), 6.91 (1H, d, J = 8.0 Hz), 5.14 (2H, s), 2.29 (3H, s), 0.31
19 (9H, s).

20 1-(4-Ethynyl-2-methyl-benzyl)-1H-imidazole (**Intermediate 141**)

21 Using General Procedure E; 1-(2-methyl-4-trimethylsilanylethynyl-
22 benzyl)-1H-imidazole (**Intermediate 140**, 140.0 mg, 0.53 mmols) in methanol
23 (5 mL) was treated with potassium carbonate (100.0 mg, 0.72 mmol) and
24 stirred overnight at ambient temperature. The crude alkyne (105 mg, 100%)
25 was used directly in the next reaction.
26 ¹H NMR (CDCl₃) δ: 7.49 (1H, s), 7.35 (1H, s), 7.31 (1H, dd, J = 1.7, 7.9 Hz),
27 7.10 (1H, s), 6.69 (1H, d, J = 7.9 Hz), 6.85 (1H, t, J = 1.2 Hz), 5.14 (2H, s),
28 3.08 (1H, s), 2.26 (3H, s).

1 Methyl [4-(4-imidazol-1-yl-methyl-3-methyl-phenylethynyl)-phenyl]-acetate
2 **(Compound 120, General Formula 6)**

3 Using General Procedure F; 1-(4-ethynyl-2-methyl-benzyl)-1*H*-
4 imidazole (**Intermediate 141**, 101.0 mg, 0.53 mmol) and methyl-(4-
5 iodophenyl)-acetate (**Reagent B**, 145.0 mg, 0.53 mmol) in triethylamine (5
6 mL) was treated with copper(I)iodide (34.0 mg, 0.18 mmol) and sparged with
7 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (124 mg,
8 0.18 mmol) was added and the reaction mixture was stirred overnight at room
9 temperature. Column chromatography (5% MeOH-EtOAc) afforded 45.0 mg
10 (25%) of the title compound as an orange oil.

11 ¹H NMR (CDCl₃) δ: 7.47 (3H, m), 7.35 (3H, m), 7.27 (3H, m), 6.91 (1H, d, J =
12 7.3 Hz), 5.11 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 2.26 (3H, s).

13 [4-(4-Imidazol-1-yl-methyl-3-methyl-phenylethynyl)-phenyl]-acetic acid
14 **(Compound 121, General Formula 6)**

15 Using General Procedure I; a solution of methyl [4-(4-imidazol-1-
16 ylmethyl-3-methyl-phenylethynyl)-phenyl]-acetate (**Compound 120**, 45.0 mg,
17 0.13 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was treated with
18 NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred
19 overnight at room temperature. Work-up afforded 30.0 mg (70%) of the title
20 compound as a pale-orange solid.

21 ¹H NMR (d₄-MeOH) δ: 8.97 (1H, s), 7.60 (2H, d J = 8.8 Hz), 7.47 (3H, m),
22 7.41 (1H, d, J = 7.9 Hz), 7.30 (2H, d, J = 7.9 Hz), 7.23 (1H, d, J = 7.9 Hz),
23 5.51 (2H, s), 3.64 (2H, s), 2.33 (3H, s).

24 1-Isopropyl-3-methoxy-benzene (Intermediate 142)

25 To a solution of 3-isopropyl-phenol (5.00 g, 36.2 mmols) in 50 mL of
26 acetone was added K₂CO₃ (7.50 g, 54.3 mmols) and iodomethane (10.3 g, 72.5
27 mmols). The resulting solution was heated to 50 °C and stirred for 18 hours,
28 cooled to room temperature, and concentrated under reduced pressure. The

1 residual oil was dissolved in Et₂O and washed with H₂O, saturated aqueous
2 NaHCO₃, and saturated aqueous NaCl before being dried (MgSO₄) and
3 concentrated under reduced pressure. The crude methyl ether was used
4 without further purification.
5 ¹H NMR (CDCl₃) δ: 7.22 (1H, t, J = 8.1 Hz), 6.84-6.72 (3H, m), 3.81 (3H, s),
6 2.88 (1H, septet, J = 7.0 Hz), 1.25 (6H, d, J = 7.0 Hz).

7 1-Bromo-2-isopropyl-4-methoxy-benzene (Intermediate 143)

8 A mixture of 1-isopropyl-3-methoxy-benzene (Intermediate 142, 3.50
9 g, 23.3 mmols), molecular sieves, and silica gel in 150 mL CCl₄ was treated
10 with *N*-bromosuccinimide (4.98 g, 28.0 mmols) at 35 °C for 18 hours. An
11 additional portion of *N*-bromosuccinimide (830.0 mg, 4.46 mmols) was added
12 and stirring continued for 6 hours. The mixture was cooled to room
13 temperature, H₂O was added, and the mixture was filtered to remove the
14 solids. The mixture was extracted with Et₂O and the combined organic layers
15 were washed with 10% aqueous HCl, H₂O, saturated aqueous NaHCO₃, and
16 saturated NaCl before being dried (MgSO₄) and concentrated under reduced
17 pressure. Column chromatography (2.5% EtOAc-hexanes) afforded 4.34 g
18 (81%) of the title compound as a pale-yellow oil.
19 ¹H NMR (CDCl₃) δ: 7.41 (1H, d, J = 8.8 Hz), 6.82 (1H, d, J = 2.6 Hz), 6.61
20 (1H, dd, J = 2.6, 8.8 Hz), 3.79 (3H, s), 3.31 (1H, septet, J = 6.7 Hz), 1.23 (6H,
21 d, J = 6.7 Hz).

22 4-Bromo-3-isopropyl-phenol (Intermediate 144)

23 To a solution of 1-bromo-2-isopropyl-4-methoxy-benzene
24 (Intermediate 143, 2.20 g, 9.60 mmols) in 50 mL CH₂Cl₂ at -78 °C was added
25 BBr₃ (4.81 g, 19.2 mmols; 19.2 mL of a 1M solution in CH₂Cl₂). After stirring
26 for 3 hours at -78 °C the solution was warmed to 0 °C for 3 hours and then at
27 25 °C for 1 hour before being quenched with H₂O. The mixture was diluted
28 with Et₂O and washed with H₂O and saturated aqueous NaCl, dried (Na₂SO₄)

1 and concentrated under reduced pressure. Column chromatography (2.5-10%
2 EtOAc-hexanes) afforded the title compound as a colorless oil.
3 ¹H NMR (CDCl₃) δ: 7.38 (1H, d, J = 8.5 Hz), 6.79 (1H, d, J = 2.9 Hz), 6.57
4 (1H, dd, J = 2.9, 8.5 Hz), 3.31 (1H, septet, J = 7.0 Hz), 1.22 (6H, d, J = 7.0
5 Hz).

6 (4-Bromo-3-isopropyl-phenoxy)-tert-butyl-dimethyl-silane (Intermediate
7 145)

8 A solution of 4-bromo-3-isopropyl-phenol (Intermediate 144, 1.13 g,
9 5.25 mmols), chloro-tert-butyl-dimethylsilane (0.95 g, 6.30 mmols), and
10 imidazole (428.0 mg, 6.3 mmols) in 10 mL DMF was stirred at 25 °C for 3
11 hours. The solution was diluted with H₂O and extracted with Et₂O and the
12 combined organic layers were washed with H₂O, saturated aqueous NaCl, and
13 dried (MgSO₄) before being concentrated under reduced pressure. Column
14 chromatography (1-2% EtOAc-hexanes) afforded 1.50 g (87%) of the title
15 compound as a colorless oil.

16 ¹H NMR (CDCl₃) δ: 7.32 (1H, d, J = 8.8 Hz), 6.73 (1H, d, J = 3.0 Hz), 6.52
17 (1H, dd, J = 3.0, 8.8 Hz), 3.26 (1H, septet, J = 6.7 Hz), 1.19 (6H, d, J = 6.7
18 Hz), 0.96 (9H, s), 0.17 (6H, s).

19 4-(Tert-butyl-dimethyl-silanyloxy)-2-isopropyl-benzaldehyde (Intermediate
20 146)

21 A solution of (4-bromo-3-isopropyl-phenoxy)-tert-butyl-dimethyl-
22 silane (Intermediate 145, 1.03 g, 3.13 mmols) in 25 mL Et₂O was cooled to -
23 78 °C and treated with tert-butyllithium (401.0 mg, 6.26 mmols; 3.7 mL of a
24 1.7M solution in pentane). After 30 minutes the reaction was quenched with
25 DMF (913.0 mg, 12.5 mmols) and warmed to room temperature. The solution
26 was diluted with H₂O, extracted with Et₂O and the combined organic layers
27 washed with H₂O and saturated aqueous NaCl before being dried (MgSO₄) and
28 concentrated under reduced pressure. Column chromatography (2% EtOAc-

1 hexanes) afforded 480.0 mg (55%) of the title compound as a colorless oil.
2 ¹H NMR (CDCl₃) δ: 10.19 (1H, s), 7.72 (1H, d, J = 8.5 Hz), 6.85 (1H, d, J =
3 2.3 Hz), 6.77 (1H, dd, J = 2.3, 8.5 Hz), 3.97 (1H, septet, J = 6.7 Hz), 1.27 (6H,
4 d, J = 6.7 Hz), 1.00 (9H, s), 0.25 (6H, s).

5 4-Hydroxy-2-isopropyl-benzaldehyde (**Intermediate 147**)

6 To a solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-2-isopropyl-
7 benzaldehyde (**Intermediate 146**, 880.0 mg, 3.17 mmols) in 6 mL THF at 0
8 °C was added tetrabutylammonium fluoride (1.66 g, 6.33 mmols; 6.3 mL of a
9 1M solution in THF). The pale-yellow solution was stirred for 30 minutes and
10 quenched by the addition of ice cold H₂O. The mixture was extracted with
11 Et₂O and the combined organic layers were washed with H₂O and saturated
12 aqueous NaCl before being dried (Na₂SO₄) and concentrated under reduced
13 pressure. Column chromatography (20% EtOAc-hexanes) afforded 500.0 mg
14 (96%) of the title compound as a colorless solid.

15 ¹H NMR (CDCl₃) δ: 10.15 (1H, s), 7.79 (1H, d, J = 8.5 Hz), 6.95 (1H, d, J =
16 2.3 Hz), 6.86 (1H, dd, J = 2.3, 8.5 Hz), 3.96 (1H, septet, J = 6.7 Hz), 1.29 (6H,
17 d, J = 6.7 Hz).

18 4-Formyl-3-isopropyl-phenyl 1,1,1-trifluoro-methansulfonate (**Intermediate**
19 **148**)

20 A solution of 4-hydroxy-2-isopropyl-benzaldehyde (**Intermediate 147**,
21 300.0 mg, 1.83 mmol) in 10 mL of CH₂Cl₂ was cooled to 0 °C and to it was
22 added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (754.0 mg,
23 1.92 mmol) and triethylamine (592.0 mg, 5.85 mmols). The resulting solution
24 was warmed to room temperature and stirred for 4.5 hours. The reaction was
25 quenched by the addition of H₂O and the mixture extracted with EtOAc and
26 the combined organic layers were washed with 10% aqueous HCl, saturated
27 aqueous NaHCO₃, H₂O, and saturated aqueous NaCl. The solution was dried
28 (MgSO₄) and concentrated under reduced pressure. The title compound was

1 isolated by column chromatography (5-10% EtOAc-hexanes) as a colorless
2 oil, 470.0 mg (87%).
3 ¹H NMR (CDCl₃) δ: 10.37 (1H, s), 7.94 (1H, d, J = 8.5 Hz), 7.33 (1H, d, J =
4 2.3 Hz), 7.26 (1H, dd, J = 2.3, 8.5 Hz), 4.00 (1H, septet, J = 6.7 Hz), 1.33 (6H,
5 d, J = 6.7 Hz),

6 4-Hydroxymethyl-3-isopropyl-phenyl 1,1,1-trifluoro-methansulfonate
7 (Intermediate 149)

8 To a solution of 4-formyl-3-isopropyl-phenyl 1,1,1-trifluoro-
9 methansulfonate (Intermediate 148, 540.0 mg, 1.82 mmols) in 7 mL MeOH
10 at 0 °C was added NaBH₄ (72.0 mg, 1.91 mmols). After stirring 2 hours at 0
11 °C the reaction was carefully quenched with H₂O and extracted with Et₂O.
12 The combined organic layers were washed with H₂O and saturated aqueous
13 NaCl, dried (MgSO₄), and concentrated under reduced pressure. The title
14 compound was isolated by column chromatography (5-10% EtOAc-hexanes)
15 as a colorless oil, 355.0 mg (90%).
16 ¹H NMR (CDCl₃) δ: 7.45 (1H, d, J = 8.5 Hz), 7.17 (1H, d, J = 2.7 Hz), 7.08
17 (1H, dd, J = 2.7, 8.5 Hz), 4.74 (2H, d, J = 5.3 Hz), 3.21 (1H, septet, J = 7.0
18 Hz), 2.12 (1H, t, J = 5.3 Hz), 1.24 (6H, d, J = 7.0 Hz).

19 4-(Tert-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-phenyl 1,1,1-trifluoro-
20 methansulfonate (Intermediate 150)

21 A solution of 4-hydroxymethyl-3-isopropyl-phenyl 1,1,1-trifluoro-
22 methansulfonate (Intermediate 149, 760.0 mg, 2.55 mmols), chloro-*tert*-
23 butyl-dimethylsilane (470.0 mg, 3.18 mmols), and imidazole (225.0 mg, 3.25
24 mmols) in 6 mL DMF was stirred at 25 °C for 17 hours. The solution was
25 diluted with H₂O and extracted with Et₂O and the combined organic layers
26 were washed with 10% aqueous HCl, saturated aqueous NaHCO₃, H₂O, and
27 saturated aqueous NaCl, and dried (MgSO₄) before being concentrated under
28 reduced pressure. Column chromatography (2-5% EtOAc-hexanes) afforded

1 970.0 mg (92%) of the title compound as a colorless oil.

2 ¹H NMR (CDCl₃) δ: 7.49 (1H, d, J = 8.5 Hz), 7.10 (1H, d, J = 2.3 Hz), 7.06
3 (1H, dd, J = 2.3, 8.5 Hz), 4.75 (2H, s), 3.10 (1H, septet, J = 6.7 Hz), 1.21 (6H,
4 d, J = 6.7 Hz), 0.93 (9H, s), 0.10 (6H, s).

5 1-(*Tert*-butyl-dimethyl-silanyloxymethyl)-2-isopropyl-4-
6 trimethylsilanylethynyl-benzene (Intermediate 151)

7 To a solution of 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-
8 phenyl 1,1,1-trifluoro-methanesulfonate (**Intermediate 150**, 970.0 mg, 2.35
9 mmols) in triethylamine (2 mL) and 6 mL DMF was sparged with argon for 15
10 minutes. Trimethylsilyl acetylene (1.00 g, 10.6 mmols) was then added
11 followed by dichlorobis(triphenylphosphine)palladium(II) (66.0 mg, 0.09
12 mmol). The resulting reaction mixture was heated to 95 °C for 20 hours. The
13 solution was cooled to room temperature and concentrated under reduced
14 pressure. The title compound (200.0 mg, 78%) was isolated by
15 chromatography (0-25% EtOAc-hexanes) as an orange oil.

16 ¹H NMR (CDCl₃) δ: 7.37-7.25 (3H, m), 4.75 (2H, s), 3.08 (1H, septet, J = 7.0
17 Hz), 1.21 (6H, d, J = 7.0 Hz), 0.92 (9H, s), 0.25 (9H, s), 0.09 (6H, s).

18 *Tert*-butyl-(4-ethynyl-2-isopropyl-benzyloxy)-dimethyl-silane (Intermediate
19 152)

20 Using General Procedure E; 1-(*tert*-butyl-dimethyl-silanyloxymethyl)-
21 2-isopropyl-4-trimethylsilanylethynyl-benzene (**Intermediate 151**, 850.0 mg,
22 2.36 mmols) in methanol (25 mL) was treated with potassium carbonate
23 (250.0 mg, 1.81 mmols) and stirred overnight at ambient temperature. The
24 crude alkyne (650 mg, 95%) was used directly in the next reaction.

25 ¹H NMR (CDCl₃) δ: 7.41-7.25 (3H, m), 4.77 (2H, s), 3.07 (1H, septet, J = 7.0
26 Hz), 3.05 (1H, s), 1.22 (6H, d, J = 7.0 Hz), 0.94 (9H, s), 0.11 (6H, s).

27 Ethyl 4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-
28 phenylethynyl]-benzoate (Intermediate 153)

1 Using General procedure F; *tert*-butyl-(4-ethynyl-2-isopropyl-
2 benzyloxy)-dimethyl-silane (**Intermediate 152**, 300.0 mg, 1.04 mmols) and
3 ethyl-4-iodo benzoate (**Reagent A**, 287.0 mg, 1.04 mmols) in triethylamine
4 (8mL) was treated with copper(I)iodide (50.0 mg, 0.26 mmol) and sparged
5 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (182
6 mg, 0.26 mmol) was added and the reaction mixture was stirred overnight at
7 room temperature. Column chromatography (2-4% EtOAc - hexanes)
8 afforded 310.0 mg (68%) of the title compound as an orange solid. .
9 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.48-
10 7.37 (3H, m), 4.80 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 3.14 (1H, septet, J = 6.8
11 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.27 (6H, d, J = 6.8 Hz), 0.96 (9H, s), 0.12 (6H,
12 s).

13 Methyl {4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-
14 phenylethynyl]-phenyl}-acetate (**Intermediate 154**)

15 Using General Procedure F; *tert*-butyl-(4-ethynyl-2-isopropyl-
16 benzyloxy)-dimethyl-silane (**Intermediate 152**, 355.0 mg, 1.26 mmols) and
17 methyl-(4-iodophenyl)-acetate (**Reagent B**, 349.0 mg, 1.26 mmols) in
18 triethylamine (8 mL) was treated with copper(I)iodide (60.0 mg, 0.32 mmol)
19 and sparged with argon for 5 minutes.
20 Dichlorobis(triphenylphosphine)palladium(II) (222 mg, 0.32 mmol) was added
21 and the reaction mixture was stirred overnight at room temperature. Column
22 chromatography (2-5% EtOAc-hexanes) afforded 288.0 mg (66%) of the title
23 compound as an orange oil.
24 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.5 Hz), 7.43-7.35 (3H, m), 7.25 (2H, d, J
25 = 8.5 Hz), 4.77 (2H, s), 3.69 (3H, s), 3.63 (2H, s), 3.11 (1H, septet, J = 6.7
26 Hz), 1.25 (6H, d, J = 6.7 Hz), 0.94 (9H, s), 0.10 (6H, s).
27 Ethyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-benzoate
28 (**Compound 122, General Formula 6**)

1 To a solution of ethyl 4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-
2 isopropyl-phenylethynyl]-benzoate (**Intermediate 153**, 310.0 mg, 0.71 mmol)
3 in 4 mL THF at 0 °C was added tetrabutylammonium fluoride (371.0 mg, 1.42
4 mmols; 1.4 mL of a 1M solution in THF). The pale-yellow solution was
5 stirred for 10 minutes and quenched by the addition of ice cold H₂O. The
6 mixture was extracted with Et₂O and the combined organic layers were
7 washed with H₂O and saturated aqueous NaCl before being dried (Na₂SO₄)
8 and concentrated under reduced pressure. Column chromatography (20-30%
9 EtOAc-hexanes) afforded 200.0 mg (87%) of the title compound as a colorless
10 solid.

11 ¹H NMR (CDCl₃) δ: 7.98 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 7.48
12 (1H, s), 7.35 (2H, m), 4.71 (2H, s), 4.35 (2H, q, J = 7.1 Hz), 3.19 (1H, septet, J
13 = 7.0 Hz), 2.51 (1H, s), 1.39 (3H, t, J = 7.1 Hz), 1.25 (6H, d, J = 7.0 Hz).

14 Methyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate
15 (**Compound 123**, General Formula 6)

16 To a solution of methyl {4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-
17 3-isopropyl-phenylethynyl]-phenyl}-acetate (**Intermediate 154**, 288.0 mg,
18 0.66 mmol) in 5 mL THF at 0 °C was added tetrabutylammonium fluoride
19 (471.0 mg, 1.80 mmols; 1.8 mL of a 1M solution in THF). The pale-yellow
20 solution was stirred for 15 minutes and quenched by the addition of ice cold
21 H₂O. The mixture was extracted with Et₂O and the combined organic layers
22 were washed with H₂O and saturated aqueous NaCl before being dried
23 (Na₂SO₄) and concentrated under reduced pressure. Column chromatography
24 (5-10% EtOAc-hexanes) afforded 180.0 mg (85%) of the title compound as a
25 colorless solid.

26 ¹H NMR (CDCl₃) δ: 7.48 (3H, m), 7.32 (2H, m), 7.24 (2H, d, J = 8.5 Hz), 4.69
27 (2H, s), 3.68 (3H, s), 3.62 (2H, s), 3.18 (1H, septet, J = 7.0 Hz), 2.21 (1H, s),
28 1.25 (6H, d, J = 7.0 Hz).

1 Ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-benzoate

2 **(Intermediate 155)**

3 A solution of ethyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-
4 benzoate (**Compound 122**, 200.0 mg, 0.62 mmol) and triphenylphosphine
5 (211.0 mg, 0.81 mmol) in 5 mL CH₂Cl₂ was cooled to 0 °C and *N*-
6 bromosuccinimide (144.0 mg, 0.81 mmol) was added in 5 portions over 20
7 minutes. The solution was warmed to 25 °C and stirred for 17 hours. The
8 reaction was quenched by the addition of dilute aqueous NaHCO₃. The
9 resulting mixture was extracted with Et₂O and the combined organic layers
10 were washed with H₂O and saturated aqueous NaCl before being dried
11 (Na₂SO₄) and concentrated under reduced pressure. The title compound, 220.0
12 mg (93%), was isolated by column chromatography (5% EtOAc-hexanes) as a
13 pale-yellow solid.

14 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.48
15 (1H, s), 7.31 (2H, m), 4.55 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 3.29 (1H, septet, J
16 = 7.0 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.30 (6H, d, J = 7.0 Hz).

17 Methyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate

18 **(Intermediate 156)**

19 A solution of methyl [4-(4-hydroxymethyl-3-isopropyl-
20 phenylethynyl)-phenyl]-acetate (**Compound 123**, 180.0 mg, 0.56 mmol) and
21 triphenylphosphine (190.0 mg, 0.73 mmol) in 5 mL CH₂Cl₂ was cooled to 0
22 °C and *N*-bromosuccinimide (130.0 mg, 0.73 mmol) was added in 5 portions
23 over 20 minutes. The solution was warmed to 25 °C and stirred for 17 hours.
24 The reaction was quenched by the addition of dilute aqueous NaHCO₃. The
25 resulting mixture was extracted with Et₂O and the combined organic layers
26 were washed with H₂O and saturated aqueous NaCl before being dried
27 (Na₂SO₄) and concentrated under reduced pressure. The title compound, 212.0
28 mg (98%), was isolated by column chromatography (5-10% EtOAc-hexanes)

1 as a pale-yellow oil.

2 ¹H NMR (CDCl₃) δ: 7.48 (3H, m), 7.28 (4H, m), 4.55 (2H, s), 3.69 (3H, s),
3 3.63 (2H, s), 3.28 (1H, septet, J = 7.0 Hz), 1.30 (6H, d, J = 7.0 Hz).

4 Ethyl [4-(4-imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-
5 benzoate (**Compound 124, General Formula 6**)

6 A solution of ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-
7 benzoate (**Intermediate 155**, 120.0 mg, 0.31 mmol) and 1-acetylimidazole
8 (36.0 mg, 0.33 mmol) in 5 mL CH₃CN was heated at 65 °C for 4 hours and
9 then at 55 °C for 16 hours. The solution was cooled to room temperature,
10 diluted with H₂O and made basic by addition of Na₂CO₃, and extracted with
11 EtOAc. The combined organic layers were washed with H₂O and saturated
12 aqueous NaCl, dried (MgSO₄), and concentrated under reduced pressure.
13 Column chromatography (1% Et₃N in 5% MeOH-EtOAc) afforded 75.0 mg
14 (65%) of the title compound as a colorless solid.

15 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.53
16 (1H, d, J = 1.5 Hz), 7.49 (1H, s), 7.35 (1H, dd, J = 1.5, 7.9 Hz), 7.09 (1H, bs),
17 6.98 (1H, d, J = 7.9 Hz), 6.85 (1H, bs), 5.19 (2H, s), 4.39 (2H, q, J = 7.1 Hz),
18 3.08 (1H, septet, J = 6.8 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.20 (6H, d, J = 6.8 Hz).

19 Methyl [4-(4-imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-
20 acetate (**Compound 125, General Formula 6**)

21 A solution of methyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-
22 phenyl]-acetate (**Intermediate 156**, 72.0 mg, 0.19 mmol) and 1-
23 acetylimidazole (22.0 mg, 0.20 mmol) in 5 mL CH₃CN was heated at 65 °C
24 for 8h and then at 55 °C for 16 hours. The solution was cooled to room
25 temperature, diluted with H₂O and made basic by addition of Na₂CO₃, and
26 extracted with EtOAc. The combined organic layers were washed with H₂O
27 and saturated aqueous NaCl, dried (MgSO₄), and concentrated under reduced
28 pressure. Column chromatography (0.5% Et₃N in 5% MeOH-EtOAc) afforded

1 40.0 mg (58%) of the title compound as a colorless solid.

2 ¹H NMR (CDCl₃) δ: 7.49 (4H, m), 7.33 (1H, dd, J = 1.5, 7.9 Hz), 7.28 (2H, d,
3 J = 8.5 Hz), 7.08 (1H, t, J = 1.2 Hz), 6.95 (1H, d, J = 7.9 Hz), 6.84 (1H, t, J =
4 1.2 Hz), 5.17 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 3.06 (1H, septet, J = 6.8 Hz),
5 1.20 (6H, d, J = 6.8 Hz).

6 [4-(4-Imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-benzoic acid
7 (Compound 126, General Formula 6)

8 Using General Procedure I; a solution of ethyl [4-(4-imidazol-1-
9 ylmethyl-3-isopropyl-phenylethynyl)-phenyl]-benzoate (Compound 124, 75.0
10 mg, 0.20 mmol) in ethanol (4 mL) and tetrahydrofuran (1 mL) was treated
11 with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and
12 stirred overnight at room temperature. Work-up afforded 68.0 mg (88%) of
13 the title compound as a colorless solid.

14 ¹H NMR (d₄-MeOH) δ: 9.01 (1H, s), 8.01 (2H, d, J = 8.2 Hz), 7.63-7.57 (5H,
15 m), 7.44 (1H, d, J = 7.9 Hz), 7.29 (1H, d, J = 7.9 Hz), 5.59 (2H, s), 3.17 (1H,
16 septet, J = 6.8 Hz), 1.20 (6H, d, J = 6.8 Hz).

17 [4-(4-Imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-acetic acid
18 (Compound 127, General Formula 6)

19 Using General Procedure I; a solution of methyl [4-(4-imidazol-1-
20 ylmethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate (Compound 125, 40.0
21 mg, 0.11 mmol) in ethanol (4 mL) and tetrahydrofuran (1 mL) was treated
22 with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and
23 stirred overnight at room temperature. Work-up afforded 22.0 mg (52%) of
24 the title compound as a colorless solid.

25 ¹H NMR (d₄-MeOH) δ: 9.02 (1H, bs), 7.62 (1H, t, J = 1.4 Hz), 7.58 (2H, m),
26 7.49 (2H, d, J = 8.2 Hz), 7.43 (1H, dd, J = 1.5, 7.9 Hz), 7.31 (3H, m), 5.58
27 (2H, s), 3.68 (2H, s), 3.16 (1H, septet, J = 6.7 Hz), 1.18 (6H, d, J = 6.7 Hz).

28 4-Bromo-N-cyclopropyl-2-methyl-benzamide (Intermediate 157)

1 A solution of 4-bromo-2-methylbenzoic acid and SOCl_2 was refluxed
2 for 3 hours, cooled to room temperature and concentrated under reduced
3 pressure. The residue was dissolved in 30 mL CH_2Cl_2 and combined with
4 cyclopropyl amine (810.0 mg, 14.3 mmols) and pyridine (2.05 g, 26.0 mmols).
5 The solution was stirred for 18 hours and then diluted with EtOAc before
6 being washed with 5% aqueous HCl, saturated NaHCO_3 , and saturated
7 aqueous NaCl. The solution was dried (MgSO_4) and concentrated under
8 reduced pressure leaving the title compound as a colorless solid.
9 ^1H NMR (CDCl_3) δ : 7.34 (1H, d, $J = 2.3$ Hz), 7.28 (1H, dd, $J = 2.3, 8.2$ Hz),
10 7.13 (1H, d, $J = 8.2$ Hz), 6.10 (1H, bs), 2.85 (1H, m), 2.37 (3H, s), 0.85 (2H,
11 m), 0.59 (2H, m).

12 (4-Bromo-2-methyl-benzyl)-cyclopropyl-amine (Intermediate 158)

13 To a solution of 4-bromo-*N*-cyclopropyl-2-methyl-benzamide
14 (**Intermediate 157**, 1.81 g, 7.12 mmols) in THF (12 mL) was added
15 $\text{BH}_3 \cdot \text{SMe}_2$ (1.08 g, 14.24 mmols). The solution was heated to 60 °C for 6
16 hours, cooled to room temperature and carefully treated with saturated
17 aqueous Na_2CO_3 (30 mL) and stirred for 17 hours. This mixture was extracted
18 with EtOAc and the combined organic layers were washed with H_2O , saturated
19 aqueous NaCl before being dried (MgSO_4) and concentrated under reduced
20 pressure. The title compound was isolated by column chromatography (10-
21 15% EtOAc-hexanes).

22 ^1H NMR (CDCl_3) δ : 7.26 (2H, m), 7.12 (1H, d, $J = 7.9$ Hz), 3.76 (2H, s), 2.31
23 (3H, s), 2.14 (1H, m), 0.44 (2H, m), 0.36 (2H, m).

24 (4-Bromo-2-methyl-benzyl)-cyclopropyl-ethyl-amine (Intermediate 159)

25 A mixture of (4-bromo-2-methyl-benzyl)-cyclopropyl-amine
26 (**Intermediate 158**, 600.0 mg, 2.49 mmols), ethyl iodide (1.56 g, 10.0 mmols),
27 and K_2CO_3 (690.0 mg, 5.00 mmols) in 10 mL acetone was heated at 60 °C for
28 18 hours. The mixture was cooled to room temperature, diluted with H_2O , and

1 extracted with EtOAc. The combined organic layers were washed with H₂O
2 and saturated aqueous NaCl before being dried (MgSO₄) and concentrated
3 under reduced pressure. The title compound was isolated by column
4 chromatography (2.5% EtOAc-hexanes).
5 ¹H NMR (CDCl₃) δ: 7.23 (2H, m), 7.12 (1H, d, J = 7.6 Hz), 3.62 (2H, s), 2.56
6 (2H, q, J = 7.3 Hz), 2.29 (3H, s), 1.75 (1H, m), 1.04 (3H, t, J = 7.3 Hz), 0.39
7 (2H, m), 0.30 (2H, m).

8 Cyclopropyl-ethyl-(2-methyl-4-trimethylsilanylethynyl-benzyl)-amine
9 (**Intermediate 160**)

10 Using General Procedure D; (4-bromo-2-methyl-benzyl)-cyclopropyl-
11 ethyl-amine (**Intermediate 159**, 620.0 mg, 2.31 mmols) in triethylamine (8
12 mL) was treated with copper(I)iodide (44.0 mg, 0.23 mmol) and then sparged
13 with argon for 15 minutes. Trimethylsilylacetylene (1.04 g, 10.6 mmols) was
14 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (162.0
15 mg, 0.23 mmol). The resulting reaction mixture was heated to 70 °C for 5
16 days. The title compound (650.0 mg, 98%) was isolated by chromatography
17 (1-4% EtOAc - hexanes).
18 ¹H NMR (CDCl₃) δ: 7.32 (1H, s), 7.20 (2H, m), 3.65 (2H, s), 2.55 (2H, q, J =
19 7.3 Hz), 2.28 (3H, s), 1.74 (1H, m), 1.03 (3H, t, J = 7.3 Hz), 0.36 (2H, m), 0.27
20 (2H, m), 0.24 (9H, s).

21 Cyclopropyl-ethyl-(4-ethynyl-2-methyl-benzyl)-amine (**Intermediate 161**)

22 Using General Procedure E; cyclopropyl-ethyl-(2-methyl-4-
23 trimethylsilanylethynyl-benzyl)-amine (**Intermediate 160**, 650.0 mg, 2.30
24 mmols) in methanol (10mL) was treated with potassium carbonate (100.0 mg,
25 0.72 mmol) and stirred overnight at ambient temperature. The crude alkyne
26 (495 mg, 99%) was used directly in the next reaction.
27 ¹H NMR (CDCl₃) δ: 7.32 (1H, s), 7.21 (2H, m), 3.66 (2H, s), 3.01 (1H, s), 2.56
28 (2H, q, J = 7.3 Hz), 2.29 (3H, s), 1.76 (1H, m), 1.04 (3H, t, J = 7.3 Hz), 0.40

1 (2H, m), 0.29 (2H, m).

2 Ethyl 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-
3 benzoate (**Compound 128, General Formula 6**)

4 Using General Procedure F; cyclopropyl-ethyl-(4-ethynyl-2-methyl-
5 benzyl)-amine (**Intermediate 161**, 190.0 mg, 0.89 mmol) and ethyl-4-iodo
6 benzoate (**Reagent A**, 245.0 mg, 0.89 mmol) in triethylamine (5 mL) was
7 treated with copper(I)iodide (56.0 mg, 0.30 mmol) and sparged with argon for
8 15 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (208 mg, 0.30
9 mmol) was added and the reaction mixture was stirred overnight at room
10 temperature. Column chromatography (3-5% EtOAc - hexanes) afforded the
11 title compound.

12 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.31-
13 7.24 (3H, m), 4.38 (2H, q, J = 7.1 Hz), 3.68 (2H, s), 2.58 (2H, q, J = 7.3 Hz),
14 2.32 (3H, s), 1.77 (1H, m), 1.39 (3H, t, J = 7.1 Hz), 1.05 (3H, t, J = 7.3 Hz),
15 0.39 (2H, m), 0.31 (2H, m).

16 Methyl (4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-
17 phenyl)-acetate (**Compound 129, General Formula 6**)

18 Using General Procedure F; cyclopropyl-ethyl-(4-ethynyl-2-methyl-
19 benzyl)-amine (**Intermediate 161**, 300.0 mg, 1.41 mmols) and methyl-(4-
20 iodophenyl)-acetate (**Reagent B**, 388.0 mg, 1.41 mmols) in triethylamine (8
21 mL) was treated with copper(I)iodide (67.0 mg, 0.35 mmol) and sparged with
22 argon for 15 minutes. Dichlorobis(triphenylphosphine)palladium(II) (246 mg,
23 0.35 mmol) was added and the reaction mixture was stirred overnight at room
24 temperature. Column chromatography (5-7% EtOAc - hexanes) afforded
25 270.0 mg (53%) of the title compound as a pale-yellow oil.

26 ¹H NMR (CDCl₃) δ: 7.47 (2H, d, J = 7.9 Hz), 7.30-7.22 (5H, m), 3.70 (3H, s),
27 3.68 (2H, s), 3.63 (2H, s), 2.58 (2H, q, J = 7.3 Hz), 2.32 (3H, s), 1.77 (1H, m),
28 1.05 (3H, t, J = 7.3 Hz), 0.39 (2H, m), 0.30 (2H, m).

1 4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-benzoic
2 acid: (Compound 130, General Formula 6)

3 Using General Procedure I; a solution of ethyl 4-{4-[(cyclopropyl-
4 ethyl-amino)-methyl]-3-methyl-phenylethynyl}-benzoate (**Compound 128**,
5 130.0 mg, 0.36 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL) was
6 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)
7 and stirred overnight at room temperature. Work-up afforded 115.0 mg (96%)
8 of the title compound as a colorless solid.

9 ¹H NMR (d₆-acetone) δ: 8.05 (2H, d, J = 8.2 Hz), 7.64 (2H, d, J = 8.2 Hz),
10 7.32 (3H, m), 3.73 (2H, s), 2.59 (2H, q, J = 7.3 Hz), 2.35 (3H, s), 1.83 (1H, m),
11 1.05 (3H, t, J = 7.3 Hz), 0.38 (2H, m), 0.27 (2H, m).

12 (4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-
13 acetic acid (Compound 131, General Formula 6)

14 Using General Procedure I; a solution of methyl (4-{4-[(cyclopropyl-
15 ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-acetate (**Compound**
16 **129**, 140.0 mg, 0.39 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL) was
17 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)
18 and stirred overnight at room temperature. Work-up followed by HPLC
19 (Partisil-10 pac 10% H₂O-CH₃CN) afforded the title compound.

20 ¹H NMR (CDCl₃) δ: 7.45 (2H, d, J = 8.2 Hz), 7.25 (5H, m), 4.16 (2H, m), 3.82
21 (2H, s), 3.56 (2H, s), 2.75 (2H, q, J = 7.3 Hz), 2.30 (3H, s), 1.86 (1H, m), 1.14
22 (3H, t, J = 7.3 Hz), 0.54 (2H, m), 0.46 (2H, m).

23 Ethyl {4-(4-cyclopropylaminomethyl-3-isopropyl-phenylethynyl)-benzoate
24 (Compound 132, General Formula 6)

25 A solution of ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-
26 benzoate (**Intermediate 155**, 110.0 mg, 0.29 mmol) and cyclopropylamine
27 (420.0 mg, 7.4 mmols) in EtOH (5 mL) was stirred at 25 °C for 6 hours and
28 then concentrated under reduced pressure. The residue was dissolved in

1 EtOAc and washed with saturated aqueous NaHCO₃, H₂O and saturated
2 aqueous NaCl. The solution was dried (MgSO₄) and concentrated under
3 reduced pressure to give 103 mg (99%) of the title compound as an orange oil.
4 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.47
5 (1H, s), 7.30 (2H, m), 4.38 (2H, q, J = 7.1 Hz), 3.89 (2H, s), 3.26 (1H, septet, J
6 = 7.0 Hz), 2.17 (1H, m), 1.40 (3H, t, J = 7.1 Hz), 1.26 (6H, d, J = 7.0 Hz), 0.45
7 (2H, m), 0.39 (2H, m).

8 Ethyl 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-
9 benzoate (Compound 133, General Formula 6)

10 To a solution of ethyl {4-(4-cyclopropylaminomethyl-3-isopropyl-
11 phenylethynyl)-benzoate (Compound 132, 103.0 mg, 0.29 mmol) in 6 mL of
12 acetone was added ethyl iodide (67.0 mg, 0.43 mmol) and K₂CO₃ (79.0 mg,
13 0.57 mmol). The mixture was stirred at 60 °C for 6 hours, cooled to room
14 temperature and quenched by the addition of H₂O. The mixture was extracted
15 with EtOAc and the combined organic layers were washed with H₂O and
16 saturated aqueous NaCl before being dried (MgSO₄) and concentrated under
17 reduced pressure. Column chromatography (4-5% EtOAc - hexanes) afforded
18 68.0 mg (59%) of the title compound.

19 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.6 Hz), 7.58 (2H, d, J = 8.6 Hz), 7.44
20 (1H, s), 7.28 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.73 (2H, s), 3.55 (1H, septet, J
21 = 6.6 Hz), 2.57 (2H, q, J = 7.3 Hz), 1.75 (1H, m), 1.40 (3H, t, J = 7.1 Hz), 1.22
22 (6H, d, J = 6.6 Hz), 1.05 (3H, t, J = 7.3 Hz), 0.37 (2H, m), 0.28 (2H, m).

23 4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-
24 benzoic acid (Compound 134, General Formula 6)

25 Using General Procedure I; a solution of ethyl 4-{4-[(cyclopropyl-
26 ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-benzoate (Compound 133,
27 68.0 mg, 0.17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
28 treated with NaOH (600.0 mg, 15.0 mmols, 3.0 mL of a 5N aqueous solution)

1 and stirred overnight at room temperature and then at 55 °C for 9 hours.
2 Work-up followed by crystallization of the solid residue from hot CH₃CN
3 afforded 45.0 mg (72%) of the title compound as a pale-yellow solid.
4 ¹H NMR (d₆-acetone) δ: 8.05 (2H, d, J = 8.1 Hz), 7.66 (2H, d, J = 8.1 Hz),
5 7.49 (1H, s), 7.32 (2H, m), 3.78 (2H, s), 3.44 (1H, septet, J = 6.7 Hz), 2.59
6 (2H, q, J = 7.3 Hz), 1.80 (1H, m), 1.21 (6H, d, J = 6.7 Hz), 1.05 (3H, t, J = 7.3
7 Hz), 0.40 (2H, m), 0.26 (2H, m).

8 Methyl [4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
9 phenyl]-acetate (Compound 4, General Formula 8)

10 Using General Procedure F; 6-ethynyl-4,4-dimethyl-3,4-dihydro-2H-
11 naphthalen-1-one (Intermediate 13, 190.0 mg, 0.96 mmol) and methyl-(4-
12 iodophenyl)-acetate (Reagent B, 245.0 mg, 0.96 mmol) in triethyl amine (8
13 mL) was treated with copper(I)iodide (46 mg, 0.24 mmol) and sparged with
14 argon for 15 minutes. Dichlorobis(triphenylphosphine)palladium(II) (168 mg,
15 0.24 mmol) was added and the reaction mixture was stirred overnight at room
16 temperature. Column chromatography (10-20% EtOAc - hexanes) afforded
17 250.0 mg (75%) of the title compound as a pale-yellow solid.
18 ¹H NMR (CDCl₃) δ: 7.99 (1H, d, J = 7.9 Hz), 7.57 (1H, d, J = 1.5 Hz), 7.51
19 (2H, d, J = 8.5 Hz), 7.43 (1H, dd, J = 1.5, 7.9 Hz), 7.29 (2H, d, J = 8.5 Hz),
20 3.70 (3H, s), 3.65 (2H, s), 2.73 (2H, t, J = 7.0 Hz), 2.04 (2H, t, J = 7.0 Hz),
21 1.41 (6H, s).

22 Methyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-
23 ethynyl)-phenyl]-acetate (Compound 135, General Formula 4)

24 To a solution of methyl [4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-
25 naphthalen-2-yl-ethynyl)-phenyl]-acetate (Compound 4) in 5 mL MeOH at 0
26 °C was added NaBH₄ (18.0 mg, 0.48 mmol). The reaction was stirred at 0 °C
27 for 2 hours and then quenched by the addition of H₂O. The solution was
28 diluted with Et₂O and washed with H₂O and saturated aqueous NaCl before

1 being dried (MgSO_4) and the solvents were removed under reduced pressure.
2 Column chromatography (20-40% EtOAc-hexanes) afforded 140.0 mg (87%)
3 of the title compound as a colorless oil.
4 ^1H NMR (CDCl_3) δ : 7.49 (3H, m), 7.39 (1H, d, $J = 7.9$ Hz), 7.31 (1H, dd, $J =$
5 1.5, 7.9 Hz), 7.25 (2H, d, $J = 8.2$ Hz), 4.58 (1H, bs), 3.68 (3H, s), 3.62 (2H, s),
6 2.05 (1H, m), 1.79 (2H, m), 1.60 (1H, m), 1.33 (3H, s), 1.26 (3H, s).

7 Methyl [4-(5-imidazol-1-yl)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-
8 ylethynyl]-phenyl]-acetate (Compound 136, General Formula 4)

9 A solution of methyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-
10 naphthalen-2-ylethynyl)-phenyl]-acetate (Compound 135, 140.0 mg, 0.40
11 mmol) and carbonyldiimidazole (136.0 mg, 0.84 mmol) in 5 mL THF was
12 heated to 65 °C for 48 hours. The solution was cooled to room temperature
13 and concentrated under reduced pressure. The residue was dissolved in Et_2O
14 and washed with 5% aqueous NaOH, H_2O , and saturated aqueous NaCl before
15 being dried (Na_2SO_4) and concentrated under reduced pressure. Column
16 chromatography (5% MeOH- CH_2Cl_2) afforded 50.0 mg (31%) of the title
17 compound as a colorless solid.

18 ^1H NMR (CDCl_3) δ : 7.57 (1H, d, $J = 1.5$ Hz), 7.52-7.45 (3H, m), 7.27 (3H, m),
19 7.08 (1H, s), 6.81 (2H, m), 5.30 (1H, t, $J = 5.8$ Hz), 3.71 (3H, s), 3.65 (2H, s),
20 2.20 (2H, m), 1.75 (2H, m), 1.40 (3H, s), 1.36 (3H, s).

21 [4-(5-Imidazol-1-yl)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl]-
22 phenyl]-acetic acid (Compound 137, General Formula 4)

23 Using General Procedure I; a solution of methyl [4-(5-imidazol-1-yl-
24 8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-phenyl]-acetate
25 (Compound 136, 50.0 mg, 0.13 mmol) in ethanol (4 mL) was treated with
26 NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred
27 overnight at room temperature. Work-up afforded 40.0 mg (83%) of the title
28 compound as a pale-orange solid.

29 ^1H NMR (d_4 -MeOH) δ : 8.93 (1H, s), 7.68 (1H, s), 7.61 (1H, s), 7.54 (1H, s),

1 7.47 (2H, d, J = 8.2 Hz), 7.31 (3H, m), 6.95 (1H, d, J = 8.2 Hz), 5.83 (1H, t, J
2 = 5.8 Hz), 3.68 (1H, s), 3.63 (1H, s), 2.38 (1H, m), 2.26 (1H, m), 1.76 (2H, m),
3 1.45 (3H, s), 1.36 (3H, s).

4 Ethyl [4-(5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-
5 ethynyl)-benzoate (Compound 138, General Formula 4)

6 A solution of ethyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-
7 naphthalen-2-yl-ethynyl)-benzoate (180.0 mg, 0.52 mmol) and
8 carbonyldiimidazole (176.0 mg, 1.08 mmol) in 5 mL THF was heated to 65 °C
9 for 21 hours. The solution was cooled to room temperature and concentrated
10 under reduced pressure. The residue was dissolved in Et₂O and washed with
11 5% aqueous NaOH, H₂O, and saturated aqueous NaCl before being dried
12 (Na₂SO₄) and concentrated under reduced pressure. Column chromatography
13 (5% MeOH-CH₂Cl₂) afforded 50.0 mg (24%) of the title compound as a
14 colorless solid.

15 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 7.9 Hz), 7.59 (3H, m), 7.46 (1H, s), 7.29
16 (1H, dd, J = 1.5, 8.3 Hz), 7.09 (1H, s), 6.82 (1H, d, J = 8.2 Hz), 6.81 (1H, s),
17 5.31 (1H, t, J = 5.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.20 (2H, m), 1.75 (2H, m),
18 1.40 (9H, m).

19 [4-(5-Imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
20 benzoic acid (Compound 139, General Formula 4)

21 Using General Procedure I; a solution of ethyl [4-(5-imidazol-1-yl-8,8-
22 dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-benzoate (Compound
23 138, 50.0 mg, 0.13 mmol) in ethanol (3 mL) and tetrahydrofuran (1 mL) was
24 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
25 and stirred overnight at room temperature. Work-up afforded 40.0 mg (87%)
26 of the title compound as a colorless solid.

27 ¹H NMR (d₄-MeOH) δ: 8.92 (1H, s), 8.04 (2H, d, J = 8.2 Hz), 7.74 (1H, d, J =
28 1.5 Hz), 7.62 (3H, m), 7.57 (1H, t, J = 1.5 Hz), 7.38 (1H, dd, J = 1.5, 7.9 Hz),
29 6.97 (1H, d, J = 7.9 Hz), 5.83 (1H, t, J = 5.8 Hz), 2.33 (2H, m), 1.78 (2H, m),

1 1.47 (3H, s), 1.39 (3H, s).

2 2-Isopropyl-4-trifluoromethanesulfonyloxy-benzyl acetate (**Intermediate**
3 **162**)

4 To a solution of 4-hydroxymethyl-3-isopropylphenyl 1,1,1-
5 trifluoromethanesulfonate (**Intermediate 149**, 190.0 mg, 0.64 mmol) in 5 mL
6 CH₂Cl₂ was added acetyl chloride (75.0 mg, 0.96 mmol) and pyridine (101.0
7 mg, 1.38 mmols). After stirring for 3 hours at 25 °C the reaction was
8 quenched by the addition of H₂O and the resulting mixture extracted with
9 EtOAc. The combined organic layers were washed with H₂O and saturated
10 aqueous NaCl, dried (MgSO₄) and concentrated under reduced pressure. The
11 title compound, 182 mg (84%), was isolated from the residual oil by column
12 chromatography (5 - 10% EtOAc-hexanes) as a colorless oil.
13 ¹H NMR (CDCl₃) δ: 7.43 (1H, d, J = 8.7 Hz), 7.19 (1H, d, J = 2.7 Hz), 7.09
14 (1H, dd, J = 2.7, 8.5 Hz), 5.17 (2H, s), 3.18 (1H, septet, J = 6.7 Hz), 2.10 (3H,
15 s), 1.26 (6H, d, J = 6.7 Hz).

16 4-Isopropenyloxymethyl-3-isopropyl-phenyl 1,1,1-trifluoromethanesulfonate
17 (**Intermediate 163**)

18 Using General Procedure 1; 2-isopropyl-4-
19 trifluoromethanesulfonyloxy-benzyl acetate (**Intermediate 162**, 182.0 mg,
20 0.54 mmols), and 1.1 mL of Tebbe's Reagent (159.0 mg, 0.56 mmols) afforded
21 130.0 mg (72%) of the title compound as a colorless oil after column
22 chromatography (2-5% EtOAc-hexanes).
23 ¹H NMR (CDCl₃) δ: 7.43 (1H, d, J = 8.5 Hz), 7.18 (1H, d, J = 2.6 Hz), 7.09
24 (1H, dd, J = 2.6, 8.5 Hz), 4.75 (2H, s), 3.98 (2H, s), 3.12 (1H, septet, J = 6.7
25 Hz), 1.88 (3H, s), 1.25 (6H, d, J = Hz).

26 3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenyl 1,1,1-
27 trifluoromethanesulfonate (**Intermediate 164**)

28 Using General Procedure 2; 4-isopropenyloxymethyl-3-isopropylphenyl

1 1,1,1-trifluoromethanesulfonate (**Intermediate 163**, 130.0 mg, 0.39 mmol),
2 Et₂Zn (272.0 mg, 2.2 mmols), and CH₂I₂ (702.0 mg, 2.6 mmols) in 3.0 mL
3 Et₂O afforded 120.0 mg (89%) of the title compound as a colorless oil after
4 column chromatography (4-5% EtOAc - hexanes).
5 ¹H NMR (CDCl₃) δ: 7.39 (1H, d, J = 8.5 Hz), 7.13 (1H, d, J = 2.7 Hz), 7.05
6 (1H, dd, J = 2.7, 8.5 Hz), 4.54 (2H, s), 3.16 (1H, septet, J = 6.7 Hz), 1.47 (3H,
7 s), 1.24 (6H, d, J = 6.7 Hz), 0.86 (2H, m), 0.48 (2H, m).

8 [3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-
9 trimethylsilane (**Intermediate 165**)

10 Using General Procedure D; 3-isopropyl-4-(1-methyl-
11 cyclopropoxymethyl)-phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate**
12 **164**, 120.0 mg, 0.34mmol) in triethylamine (2 mL) and anhydrous DMF (5
13 mL) was sparged with argon for 5 minutes. Trimethylsilyl acetylene (700.0
14 mg, 0.71 mmol) was then added followed by
15 dichlorobis(triphenylphosphine)palladium(II) (24.0 mg, 0.03 mmol). The
16 resulting reaction mixture was heated to 95 °C for 60 hours. The title
17 compound 110.0 mg, (99%) was isolated by chromatography (0-1% EtOAc -
18 hexanes).
19 ¹H NMR (CDCl₃) δ: 7.36 (1H, s), 7.24 (2H, bs), 4.53 (2H, s), 3.11 (1H, septet,
20 J = 6.7 Hz), 1.45 (3H, s), 1.22 (6H, d, J = 6.7 Hz), 0.85 (2H, m), 0.44 (2H, m),
21 0.25 (9H, s).

22 4-Ethynyl-2-isopropyl-1-(1-methyl-cyclopropoxymethyl)-benzene
23 (**Intermediate 166**)

24 Using General Procedure E; [3-isopropyl-4-(1-methyl-
25 cyclopropoxymethyl)-phenylethynyl]-trimethylsilane (**Intermediate 165**,
26 110.0 mg, 0.37 mmol) in methanol (6 mL) was treated with potassium
27 carbonate (80.0 mg, 0.58 mmol) and stirred overnight at ambient temperature.
28 The crude alkyne (84 mg, 100%) was used directly in the next reaction.

1 ¹H NMR (CDCl₃) δ: 7.55 (1H, s), 7.41 (2H, m), 4.68 (2H, s), 3.26 (1H, septet,
2 J = 6.8 Hz), 3.18 (1H, s), 1.60 (3H, s), 1.37 (6H, d, J = 6.8 Hz), 0.99 (2H, m),
3 0.59 (2H, m).

4 Methyl {4-[3-isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-
5 phenyl}-acetate (Compound 140, General Formula 6)

6 Using General Procedure F; 4-ethynyl-2-isopropyl-1-(1-methyl-
7 cyclopropoxymethyl)-benzene (Intermediate 166, 78.0 mg, 0.34 mmol) and
8 methyl-(4-iodophenyl)-acetate (Reagent B, 94.0 mg, 0.34 mmol) in
9 triethylamine (8 mL) was treated with copper(I)iodide (22.0 mg, 0.11 mmol)
10 and sparged with argon for 5 minutes.
11 Dichlorobis(triphenylphosphine)palladium(II) (79 mg, 0.11 mmol) was added
12 and the reaction mixture was stirred at room temperature for 3.5 hours.
13 Column chromatography (2-5% EtOAc - hexanes) afforded 77.0 mg (60%) of
14 the title compound as a yellow oil.

15 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.2 Hz), 7.43 (1H, d, J = 1.5 Hz), 7.33-
16 7.24 (4H, m), 4.55 (2H, s), 3.70 (3H, s), 3.63 (2H, s), 3.14 (1H, septet, J = 6.8
17 Hz), 1.47 (3H, s), 1.25 (6H, d, J = 6.8 Hz), 0.86 (2H, m), 0.46 (2H, m).

18 {4-[3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-
19 acetic acid (Compound 141, Formula 6)

20 Using General Procedure I; a solution methyl {4-[3-isopropyl-4-(1-
21 methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-acetate (Compound
22 140, 70.0 mg, 0.19 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
23 treated with NaOH (240.0 mg, 6.0 mmols, 2.0 mL of a 3N aqueous solution)
24 and stirred overnight at room temperature. Work-up and purification by
25 HPLC (Partisil 10-pac, 10% H₂O/CH₃CN) afforded of the title compound as a
26 colorless solid.

27 ¹H NMR (CDCl₃) δ: 7.50 (2H, d, J = 8.2 Hz), 7.43 (1H, s), 7.33-7.24 (4H, m),
28 4.55 (2H, s), 3.65 (2H, s), 3.14 (1H, septet, J = 6.7 Hz), 1.47 (3H, s), 1.25 (6H,

1 d, $J = 6.7$ Hz), 0.87 (2H, m), 0.46 (2H, m).

2 2,6-Di-*tert*-butyl-4-trimethylsilanylethynyl-phenol: (**Intermediate 167**)

3 Following General Procedure D and using 4-bromo-2,6-di-*t*-butyl-
4 phenol (1.43g, 5mmol), triethyl amine (15mL), anhydrous tetrahydrofuran
5 (15mL), copper(I)iodide (0.06g, 0.31mmol), trimethylsilyl acetylene (4.9g,
6 50mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.18g, 0.26mmol)
7 followed by flash column chromatography over silica gel (230-400 mesh)
8 using hexane as eluent, the title compound was obtained (1.35g, 90%).

9 ^1H NMR (300 MHz, CDCl_3): δ 7.29 (s, 2H), 5.35 (s, 1H), 1.42 (s, 18H), 0.24
10 (s, 9H).

11 (3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-trimethyl-silane: (**Intermediate**
12 **168**)

13 A solution 2,6-di-*tert*-butyl-4-trimethylsilanylethynyl-phenol
14 (**Intermediate 167**, 0.302g, 1mmol) in acetone (5mL) was treated with
15 potassium carbonate (0.138g, 1mmol) and methyl iodide (0.142g, 1mmol) and
16 stirred overnight at room temperature. The volatiles were distilled off *in*
17 *vacuo* and the residue was purified by flash column chromatography on silica
18 gel (230-400 mesh) using ethyl acetate as the eluent to afford the title
19 compound as a white solid (0.28g, 90%).

20 ^1H NMR (300 MHz, CDCl_3): δ 7.41 (s, 2H), 3.70 (s, 3H), 1.49 (s, 18H), 0.30
21 (s, 9H).

22 1,3-Di-*tert*-butyl-5-ethynyl-2-methoxy-benzene: (**Intermediate 169**)

23 Following General Procedure E and (3,5-di-*tert*-butyl-4-methoxy-
24 phenylethynyl)-trimethyl-silane (**Intermediate 168**, 0.28g, 0.9mmol),
25 potassium carbonate (0.98g, 7.1mmol) and methanol (10mL) followed by flash
26 column chromatography over silica gel (230-400 mesh) using hexane as the
27 eluent, the title compound was obtained (0.23g, 100%).

28 ^1H NMR (300 MHz, CDCl_3): δ 7.46 (s, 2H), 3.75 (s, 3H), 3.05 (s, 1H), 1.49 (s,

1 18H).

2 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid methyl
3 ester: (Compound 142, General Formula 5)

4 Following General Procedure F and using 1,3-di-*tert*-butyl-5-ethynyl-2-
5 methoxy-benzene (**Intermediate 169**, 0.094g, 0.36mmol), methyl-4-iodo
6 phenyl acetate (**Reagent B**, 0.09g, 0.32mmol), triethyl amine (5mL),
7 anhydrous tetrahydrofuran (5mL), copper(I)iodide (0.02g, 0.1mmol) and
8 dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed by
9 flash column chromatography over silica gel (230-400 mesh) using 10 % ethyl
10 acetate in hexane as the eluent, the title compound (0.114g, 81%) was obtained
11 as an oil.

12 ¹H NMR (300 MHz, CDCl₃): δ 7.52 (d, 2H, *J* = 8.0Hz), 7.46 (s, 2H), 7.28 (d,
13 2H, *J* = 8.2Hz), 3.72 (s, 3H), 3.71(s, 3H), 3.66 (s, 2H), 1.47 (s, 18H).

14 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid:
15 **(Compound 143, General Formula 5)**

16 Following General Procedure I and using [4-(3,5-di-*tert*-butyl-4-
17 methoxy-phenylethynyl)-phenyl]-acetic acid methyl ester (**Compound 142**,
18 0.114g, 0.29mmol), 5M aqueous sodium hydroxide solution (2mL) and
19 ethanol (4mL), followed by preparative reverse phase HPLC using 10% water
20 in acetonitrile as the mobile phase, the title compound was obtained as a white
21 solid (0.097g, 88%).

22 ¹H NMR (300 MHz, CDCl₃): δ 7.55(d, 2H, *J* = 8.0Hz), 7.48 (s, 2H), 7.30 (d,
23 2H, *J* = 8.2Hz), 3.74 (s, 3H), 3.69 (s, 2H), 1.49 (s, 18H).

24 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid
25 methyl ester: (Compound 144, General Formula 5)

26 Following General Procedure F and using 1,3-di-*tert*-butyl-5-ethynyl-2-
27 methoxy-benzene (**Intermediate 169**, 0.087g, 0.33mmol), methyl-2-fluoro-4-
28 iodo phenyl acetate (**Reagent H**, 0.088g, 0.30mmol), triethyl amine (5mL),
29 anhydrous tetrahydrofuran (10mL), copper(I)iodide (0.02g, 0.1mmol) and
30 dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed by

1 flash column chromatography over silica gel (230-400 mesh) using 10 % ethyl
2 acetate in hexane as the eluent, the title compound (0.122g, 89%) was
3 obtained.

4 ¹H NMR (300 MHz, CDCl₃): δ 7.46 (s, 2H), 7.33-7.24 (m, 3H), 3.75 (s, 3H),
5 3.73(s, 3H), 3.72 (s, 2H), 1.48 (s, 18H).

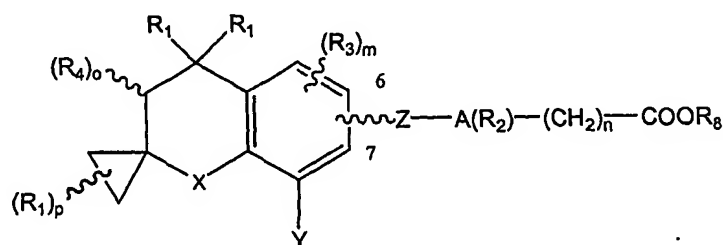
6 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid:

7 **(Compound 145, General Formula 5)**

8 Following General Procedure I and using [4-(3,5-di-*tert*-butyl-4-
9 methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid methyl ester
10 **(Compound 144, 0.122g, 0.29mmol)**, 5M aqueous sodium hydroxide solution
11 (1mL) and ethanol (4mL), followed preparative reverse phase HPLC using
12 10% water in acetonitrile as the mobile phase, the title compound was
13 obtained as a white solid (0.077g, 65%).
14 ¹H NMR (300 MHz, CDCl₃): δ 7.42 (s, 2H), 7.29-7.19 (m, 3H), 3.71 (s, 2H),
15 3.69 (s, 3H), 1.43 (s, 18H).

1 WHAT IS CLAIMED IS:

2 1. A method of inhibiting the enzyme cytochrome P450RAI in a
3 mammal by administering to said mammal an effective dose of a
4 pharmaceutical composition comprising a compound of the formula



13 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
14 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
15 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
16 groups being optionally substituted with one or two R₂ groups;

17 X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;

18 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
19 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
20 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

21 Z is -C≡C-,

22 -(CR₁=CR₁)_n, where n' is an integer having the value 1 - 5,

23 -CO-NR₁-,

24 NR₁-CO-;

25 -CO-O-,

26 -O-CO-,

27 -CS-NR₁-,

28 NR₁-CS-,

-CO-S-,

1 -S-CO-,

2 -N=N-;

3 **R₁** is independently H or alkyl of 1 to 6 carbons;

4 **p** is an integer having the values of 0 to 4;

5 **R₂** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro
6 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
7 to 6 carbons;

8 **R₃** is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
9 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
10 of 1 to 6 carbons or benzyl;

11 **m** is an integer having the values 0 to 2;

12 **R₄** is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
13 alkyl of 1 to 6 carbons, or halogen;

14 **o** is an integer having the values of 0 to 2;

15 **n** is an integer having the values of 0 to 4, and

16 **R₈** is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
17 pharmaceutically acceptable base.

18 2. A method in accordance with Claim 1 wherein the compound has
19 the formula

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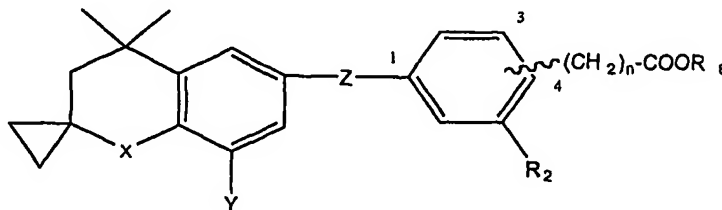
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where **X** is O or CH₃N;

Y is H or cyclopropyl;

1 **Z** is -C≡C- or -CO-O-;

2 **R₂** is H or F;

3 **n** is 0 or 1, and

4 **R₈** is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
5 acceptable base.

6 3. A method in accordance with Claim 2 wherein the compound is
7 selected from the group consisting of:

8 benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
9 cyclopropane]-6-yl)ethynyl]-, benzeneacetic acid, 4-[(3,4-dihydro-4,4-
10 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- and 2-
11 fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
12 cyclopropane]-6-yl)ethynyl]- or a salt with a pharmaceutically acceptable
13 base or a C₁₋₆ alkyl ester of said compound.

14 4. A method in accordance with Claim 2 wherein the compound is
15 selected from the group consisting of:

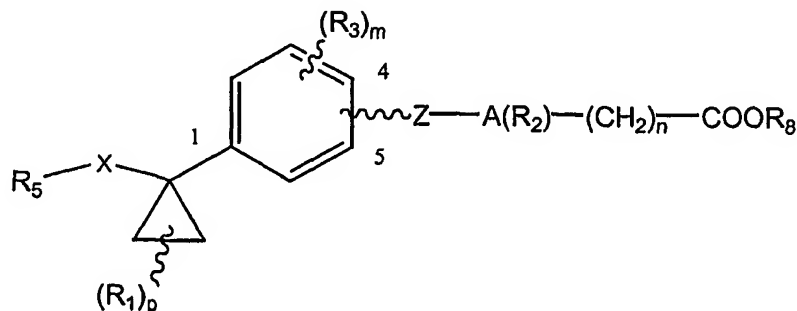
16 benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-
17 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-, 4-[(8-
18 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
19 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid, benzoic acid, 4-[(8-
20 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
21 cyclopropane]-6-yl)ethynyl]- and 4-[(8-cyclopropyl-3,4-dihydro-4,4-
22 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-2-fluoro-
23 benzoic acid or a salt with a pharmaceutically acceptable base or a C₁₋₆ alkyl
24 ester of said compound.

25 5. A method in accordance with Claim 2 wherein the compound is
26 spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-
27 3,4-dihydro-4,4-dimethyl-, 4-(carboxymethyl)phenyl ester or a salt with a
28 pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said compound.

1 6. A method in accordance with Claim 2 wherein the compound is
2 spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-
3 3,4-dihydro-4,4-dimethyl-, 3-(carboxymethyl)phenyl ester or a salt with a
4 pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said compound.

5 7. A method in accordance with Claim 2 wherein the compound is
6 benzoic acid, 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-
7 cyclopropane]-6-yl)ethynyl]- or a salt with a pharmaceutically acceptable
8 base or a C₁₋₆ alkyl ester of said compound.

9 8. A method of inhibiting the enzyme cytochrome P450RAI in a
10 mammal by administering to said mammal an effective dose of a
11 pharmaceutical composition comprising a compound of the formula
12



20 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
21 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
22 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
23 groups being optionally substituted with one or two R₂ groups;

24 X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;

25 Z is -C≡C-,

26 -(CR₁=CR₁)_n, where n' is an integer having the value 1 - 5,

27 -CO-NR₁-,

28 NR₁-CO-,

1 -CO-O-,

2 -O-CO-,

3 -CS-NR₁-,

4 NR₁-CS-,

5 -CO-S-,

6 -S-CO-,

7 -N=N-;

8 R₁ is independently H or alkyl of 1 to 6 carbons;

9 p is an integer having the values of 0 to 4;

10 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
11 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
12 to 6 carbons;

13 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
14 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
15 of 1 to 6 carbons or benzyl;

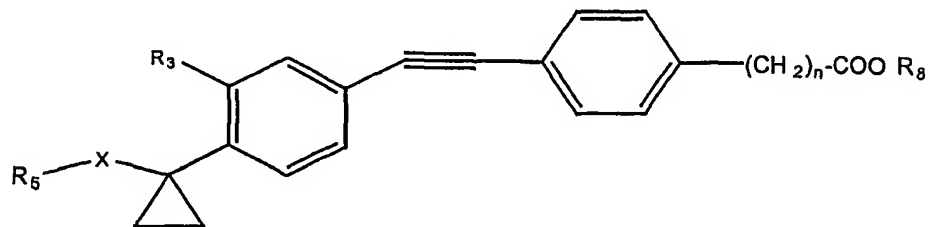
16 m is an integer having the values 0 to 4;

17 R₅ is H, alkyl of 1 to 6 carbons, fluorosubstituted alkyl of 1 to 6
18 carbons, benzyl, or lower alkyl or halogen substituted benzyl;

19 n is an integer having the values of 0 to 4, and

20 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
21 pharmaceutically acceptable base.

22 9. A method in accordance with Claim 8 wherein the compound has
23 the formula



1 where X is O, NR where R is H, *n*-propyl or benzyl;
2 R₃ is H or lower alkyl of 1 to 6 carbons;
3 R₅ is benzyl or lower alkyl of 1 to 6 carbons;
4 *n* is 0 or 1, and
5 R₈ is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
6 acceptable base.

7 10. A method in accordance with Claim 9 wherein the compound is
8 selected from the group consisting of 4-[4-(1-propylamino-cyclopropyl)-
9 phenylethynyl]-benzoic acid and 4-[4-(1-benzylamino-cyclopropyl)-
10 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable base
11 or a C₁₋₆ alkyl ester of said compound.

12 11. A method in accordance with Claim 9 wherein the compound is
13 selected from the group consisting of 4-[4-(1-dibenzylamino-cyclopropyl)-
14 phenylethynyl]-benzoic acid and 4-[4-(1-benzylmethylamino-cyclopropyl)-
15 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable base
16 or a C₁₋₆ alkyl ester of said compound.

17 12. A method in accordance with Claim 9 wherein the compound is
18 selected from the group consisting of 4-[4-(1-benzyloxycyclopropyl)-
19 phenylethynyl]-benzoic acid, 4-[4-(1-benzyloxycyclopropyl)-3-methyl-
20 phenylethynyl]-benzoic acid and 4-[4-(1-benzyloxycyclopropyl)-3-ethyl-
21 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable
22 base or a C₁₋₆ alkyl ester of said compound.

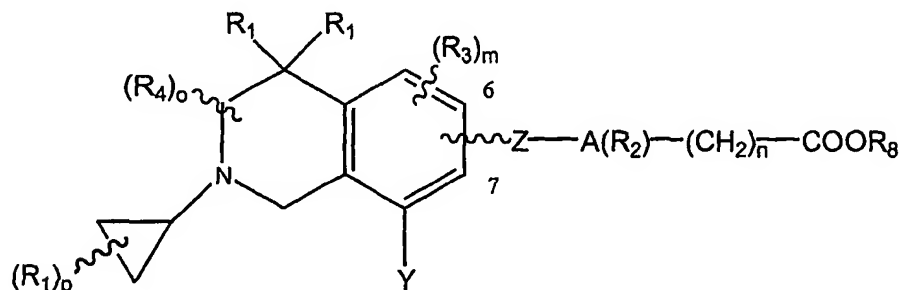
23 13. A method in accordance with Claim 9 wherein the compound is
24 selected from the group consisting of {4-[4-(1-benzyloxycyclopropyl)-
25 phenylethynyl]-phenyl}-acetic acid, {4-[4-(1-benzyloxycyclopropyl)-3-
26 methyl-phenylethynyl]-phenyl}-acetic acid and {4-[4-(1-
27 benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid or a salt
28 with a pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said

1 compound.

2 **14.** A method in accordance with Claim 9 wherein the compound is
3 selected from the group consisting of 4-[4-(1-methoxycyclopropyl)-
4 phenylethynyl]-benzoic acid, 4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-
5 benzoic acid, 4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-
6 benzoic acid, 4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-
7 phenylethynyl]-benzoic acid and 4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-
8 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable
9 base or a C₁₋₆ alkyl ester of said compound.

10 **15.** A method in accordance with Claim 9 wherein the compound is
11 selected from the group consisting of {4-[4-(1-methoxycyclopropyl)-
12 phenylethynyl]-phenyl}-acetic acid, {4-[4-(1-isopropoxycyclopropyl)-
13 phenylethynyl]-phenyl}-acetic acid, {4-[4-(1-isopropoxycyclopropyl)-3-
14 methyl-phenylethynyl]-phenyl}-acetic acid, {4-[4-[1-(2,2-
15 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-phenyl}-acetic
16 acid, {4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic
17 acid, {4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic
18 acid and {4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-
19 acetic acid or a salt with a pharmaceutically acceptable base or a C₁₋₆ alkyl
20 ester of said compound.

1 16. A method of inhibiting the enzyme cytochrome P450RAI in a
 2 mammal by administering to said mammal an effective dose of a
 3 pharmaceutical composition comprising a compound of the formula



11 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
 12 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
 13 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
 14 groups being optionally substituted with one or two R_2 groups;

15 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
 16 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
 17 to 6 carbons, lower alkyl substituted cycloalkyl of 1 to 6 carbons, Cl, Br, or I;

18 Z is $-C\equiv C-$,

19 $-(CR_1=CR_1)_n$, where n' is an integer having the value 1 - 5,

20 $-CO-NR_1-$,

21 NR_1-CO- ,

22 $-CO-O-$,

23 $-O-CO-$,

24 $-CS-NR_1-$,

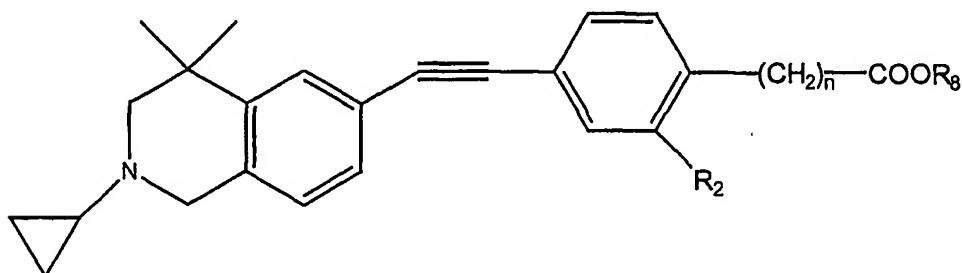
25 NR_1-CS- ,

26 $-CO-S-$,

27 $-S-CO-$,

28 $-N=N-$;

- 1 R_1 is independently H or alkyl of 1 to 6 carbons;
 2 p is an integer having the values of 0 to 5;
 3 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
 4 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
 5 to 6 carbons;
 6 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
 7 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
 8 of 1 to 6 carbons or benzyl;
 9 m is an integer having the values 0 to 2;
 10 R_4 is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
 11 alkyl of 1 to 6 carbons, or halogen;
 12 o is an integer having the values of 0 to 4;
 13 n is an integer having the values of 0 to 4, and
 14 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
 15 pharmaceutically acceptable base.
 16 17. A method in accordance with Claim 16 wherein the compound has
 17 the formula



- 18 where R_2 is H or halogen;
 19 n is 0 or 1 and
 20 R_8 is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
 21 acceptable base.
 22 18. A method in accordance with Claim 17 wherein the compound is

1 [4-(2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-
2 2-fluoro-phenyl]-acetic acid or a salt with a pharmaceutically acceptable
3 base.

4 19. A method in accordance with Claim 17 wherein the compound is
5 [4-(2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-
6 phenyl]-acetic acid or a salt with a pharmaceutically acceptable base.

7 20. A method of inhibiting the enzyme cytochrome P450RAI in a
8 mammal by administering to said mammal an effective dose of a
9 pharmaceutical composition comprising a compound of the formula

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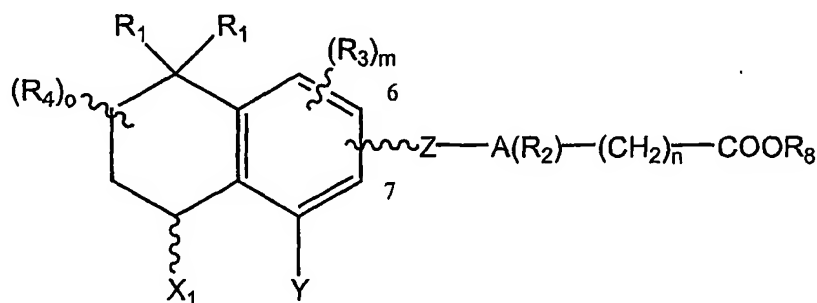
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17 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
18 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
19 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
20 groups being optionally substituted with one or two R₂ groups;

21 X₁ is 1-imidazolyl, or lower alkyl or halogen substituted 1-imidazolyl,
22 OR, SR, NRR₆ where R is H, alkyl of 1 to 6 carbons or benzyl;

23 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
24 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
25 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

26 Z is -C≡C-,

27 -(CR₁=CR₁)_n, where n' is an integer having the value 1 - 5,

28 -CO-NR₁-,

1 NR₁-CO-,

2 -CO-O-,

3 -O-CO-,

4 -CS-NR₁-,

5 NR₁-CS-,

6 -CO-S-,

7 -S-CO-,

8 -N=N-;

9 R₁ is independently H or alkyl of 1 to 6 carbons;

10 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
11 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
12 to 6 carbons;

13 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
14 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
15 of 1 to 6 carbons or benzyl;

16 m is an integer having the values 0 to 2;

17 R₄ is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
18 alkyl of 1 to 6 carbons, or halogen;

19 o is an integer having the values of 0 to 4;

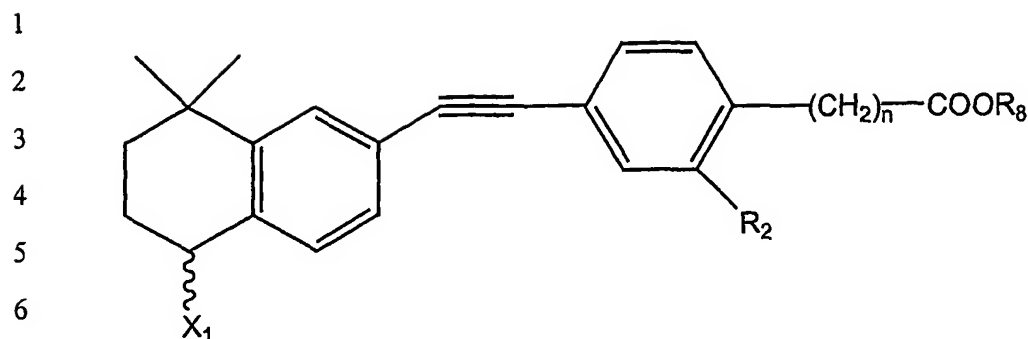
20 R₆ is H, lower alkyl, cycloalkyl of 3 to 6 carbons, lower alkyl
21 substituted cycloalkyl of 3 to 6 carbons;

22 n is an integer having the values of 0 to 4, and

23 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
24 pharmaceutically acceptable base, with the proviso that when Y is H, A is
25 phenyl and X₁ is OH then n is 1 to 4.

26 21. A method in accordance with Claim 20 wherein the compound has
27 the formula

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wherein X_1 is 1-imidazolyl, or dialkyl-N or alkyl, cyclopropyl-N where the alkyl group has 1 to 6 carbons;

R_2 is H or halogen;

n is 0 or 1, and

R_8 is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically acceptable base.

22. A method in accordance with Claim 21 where the compound is selected from the group consisting of 4-[(5-cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-benzoic acid and 4-[5-(cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid or a salt with a pharmaceutically acceptable base or a C_{1-6} alkyl ester of said compound.

23. A method in accordance with Claim 21 where the compound is selected from the group consisting of 4-[(5-(cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid and [4-(5-(cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid or a salt with a pharmaceutically acceptable base or a C_{1-6} alkyl ester of said compound.

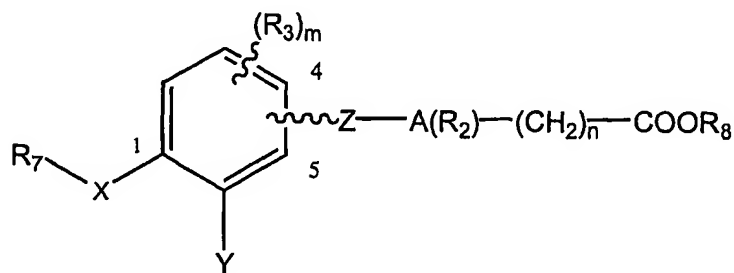
24. A method in accordance with Claim 21 where the compound is 4-[5-(*iso*-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-benzoic acid or a salt with a pharmaceutically acceptable base or

1 a C₁₋₆ alkyl ester of said compound.

2 25. A method in accordance with Claim 21 where the compound is [4-
3 (5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
4 benzoic acid or a salt with a pharmaceutically acceptable base or a C₁₋₆ alkyl
5 ester of said compound.

6 26. A method in accordance with Claim 21 where the compound is [4-
7 (5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
8 phenyl]-acetic acid or a salt with a pharmaceutically acceptable base or a C₁₋₆
9 alkyl ester of said compound.

10 27. A method of inhibiting the enzyme cytochrome P450RAI in a
11 mammal by administering to said mammal an effective dose of a
12 pharmaceutical composition comprising a compound of the formula
13
14
15



21 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group
22 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
23 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl
24 groups being optionally substituted with one or two R₂ groups;

25 X is O, S or NR where R is H, alkyl of 1 to 6 carbons, C₁₋₆-trialkylsilyl
26 or benzyl;

27 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
28 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons; cycloalkyl of 3

1 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

2 **Z** is $-\text{C}\equiv\text{C}-$,

3 $-(\text{CR}_1=\text{CR}_1)_{n'}$, where n' is an integer having the value 1 - 5,

4 $-\text{CO}-\text{NR}_1-$,

5 $\text{NR}_1-\text{CO}-$,

6 $-\text{CO}-\text{O}-$,

7 $-\text{O}-\text{CO}-$,

8 $-\text{CS}-\text{NR}_1-$,

9 $\text{NR}_1-\text{CS}-$,

10 $-\text{CO}-\text{S}-$,

11 $-\text{S}-\text{CO}-$,

12 $-\text{N}=\text{N}-$;

13 **R**₁ is independently H or alkyl of 1 to 6 carbons;

14 **R**₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
15 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
16 to 6 carbons;

17 **R**₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
18 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
19 of 1 to 6 carbons or benzyl;

20 **m** is an integer having the values 0 to 3;

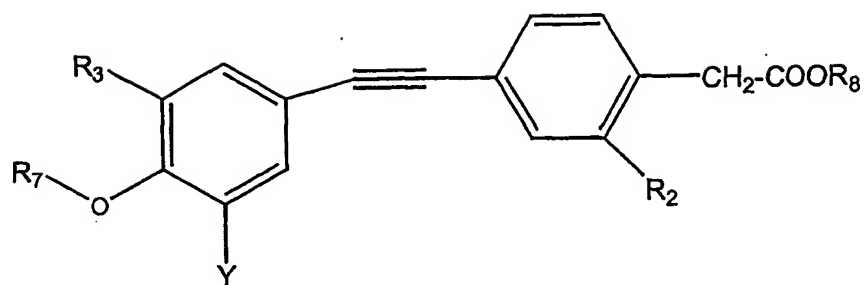
21 **R**₇ is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or lower
22 alkyl substituted cycloalkyl of 1 to 6 carbons;

23 **n** is an integer having the values of 1 to 4, and

24 **R**₈ is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
25 pharmaceutically acceptable base.

26 **28.** A method in accordance with Claim 27 wherein the compound has
27 the formula

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wherein Y is branched-chain alkyl of 3 to 6 carbons;

R_2 is H or F;

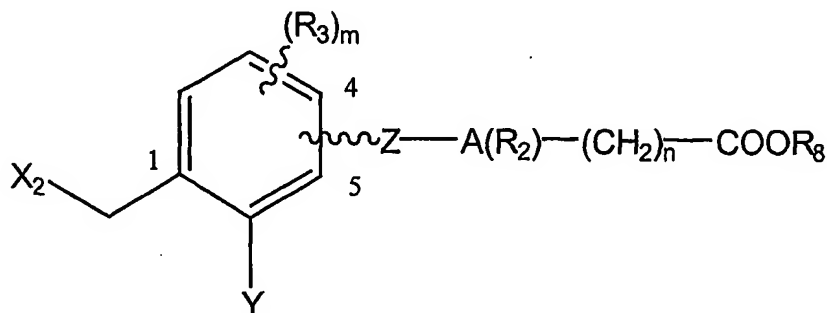
R_3 is branched-chain alkyl of 3 to 6 carbons;

R_7 is lower alkyl of 1 to 6 carbons, and

R_8 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base.

29. A method in accordance with Claim 27 where the compound is selected from the group consisting of [4-(3,5-di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid and [4-(3,5-di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid or a salt of said compound with a pharmaceutically acceptable base.

30. A method of inhibiting the enzyme cytochrome P450RAI in a mammal by administering to said mammal an effective dose of a pharmaceutical composition comprising a compound of the formula



wherein A is a phenyl or naphthyl group, or heteroaryl selected from a

1 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
2 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
3 groups being optionally substituted with one or two R_2 groups;

4 X_2 is 1-imidazolyl, lower alkyl or halogen substituted 1-imidazolyl,
5 OR_7 , SR_7 or NRR_7 where R is H, alkyl of 1 to 6 carbons or benzyl;

6 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
7 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
8 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

9 Z is $-C\equiv C-$,

10 $-(CR_1=CR_1)_n$, where n is an integer having the value 1 - 5,

11 $-CO-NR_1-$,

12 NR_1-CO- ,

13 $-CO-O-$,

14 $-O-CO-$,

15 $-CS-NR_1-$,

16 NR_1-CS- ,

17 $-CO-S-$,

18 $-S-CO-$,

19 $-N=N-$;

20 R_1 is independently H or alkyl of 1 to 6 carbons;

21 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
22 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
23 to 6 carbons;

24 R_3 is alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro substituted alkyl of 1 to
25 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio of 1 to 6 carbons or
26 benzyl;

27 m is an integer having the values 0 to 3;

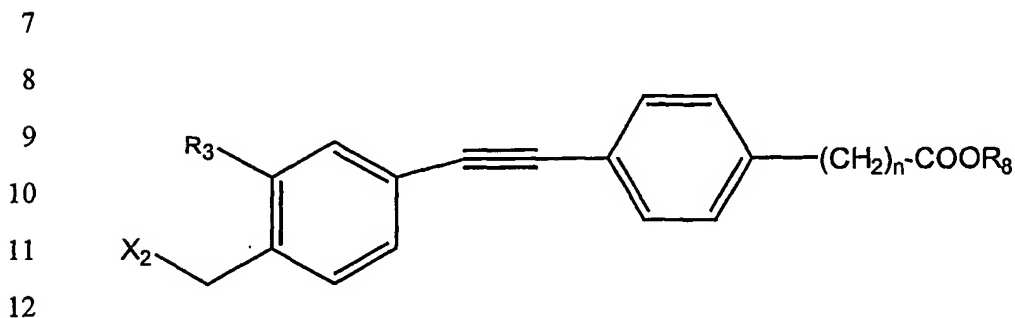
28 R_7 is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, lower

1 alkyl substituted cycloalkyl of 3 to 6 carbons or C₁₋₆-trialkylsilyl.

2 n is an integer having the values of 0 to 4, and

3 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
4 pharmaceutically acceptable base.

5 31. A method in accordance with Claim 30 where the compound has
6 the formula



13 wherein R₃ is alkyl of 1 to 6 carbons;

14 X₂ is 1-imidazolyl, OR₇, or NRR₇ where R is alkyl of 1 to 6 carbons
15 or cyclopropyl, and R₇ is alkyl of 1 to 6 carbons, cyclopropyl or lower alkyl
16 substituted cyclopropyl;

17 n is 0 or 1, and

18 R₈ is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
19 acceptable base.

20 32. A method in accordance with Claim 31 wherein the compound is
21 selected from the group consisting of 4-(4-imidazol-1-yl-methyl-3-methyl-
22 phenylethynyl)-benzoic acid and [4-(4-imidazol-1-yl-methyl-3-isopropyl-
23 phenylethynyl)-phenyl]-benzoic acid or a salt of said compound with a
24 pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said compound.

25 33. A method in accordance with Claim 31 where the compound is
26 selected from the group consisting of [4-(4-imidazol-1-yl-methyl-3-methyl-
27 phenylethynyl)-phenyl]-acetic acid and [4-(4-imidazol-1-yl-methyl-3-
28 isopropyl-phenylethynyl)-phenyl]-acetic acid or a salt of said compound with

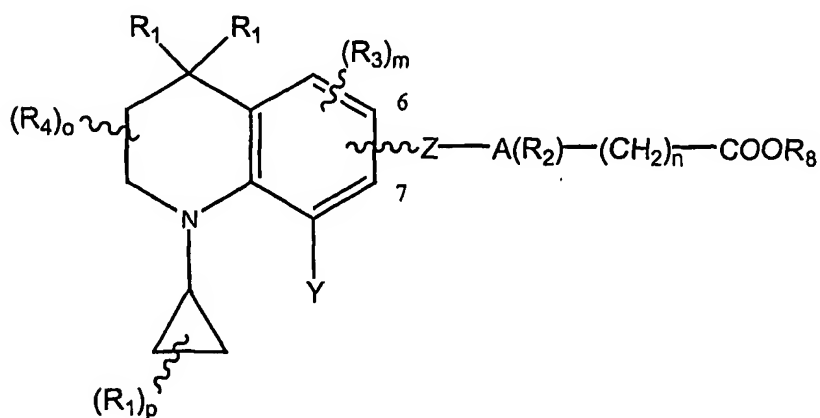
1 a pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said compound.

2 34. A method in accordance with Claim 31 where the compound is
3 selected from the group consisting of 4-{4-[(cyclopropyl-ethyl-amino)-
4 methyl]-3-methyl-phenylethynyl}-benzoic and 4-{4-[(cyclopropyl-ethyl-
5 amino)-methyl]-3-isopropyl-phenylethynyl}-benzoic acid or a salt of said
6 compound with a pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said
7 compound.

8 35. A method in accordance with Claim 31 where the compound is (4-
9 {4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-
10 acetic acid or a salt of said compound with a pharmaceutically acceptable
11 base or a C₁₋₆ alkyl ester of said compound.

12 36. A method in accordance with Claim 31 where the compound is {4-
13 [3-isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-acetic
14 acid or a salt of said compound with a pharmaceutically acceptable base or a
15 C₁₋₆ alkyl ester of said compound.

16 37. A method of inhibiting the enzyme cytochrome P450RAI in a
17 mammal by administering to said mammal as effective dose of a
18 pharmaceutical composition comprising a compound of the formula



1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
2 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
3 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
4 groups being optionally substituted with one or two R_2 groups;

5 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
6 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3
7 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, F, Cl, Br, or
8 I;

9 Z is $-C\equiv C-$,
10 $-(CR_1=CR_1)_n$, where n' is an integer having the value 1 - 5,
11 $-CO-NR_1-$,
12 NR_1-CO- ,
13 $-CO-O-$,
14 $-O-CO-$,
15 $-CS-NR_1-$,
16 NR_1-CS- ,
17 $-CO-S-$,
18 $-S-CO-$,
19 $-N=N-$;

20 R_1 is independently H or alkyl of 1 to 6 carbons;

21 p is an integer having the values of 0 to 5;

22 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro
23 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
24 to 6 carbons;

25 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro
26 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
27 of 1 to 6 carbons or benzyl;

28 m is an integer having the values 0 to 2;

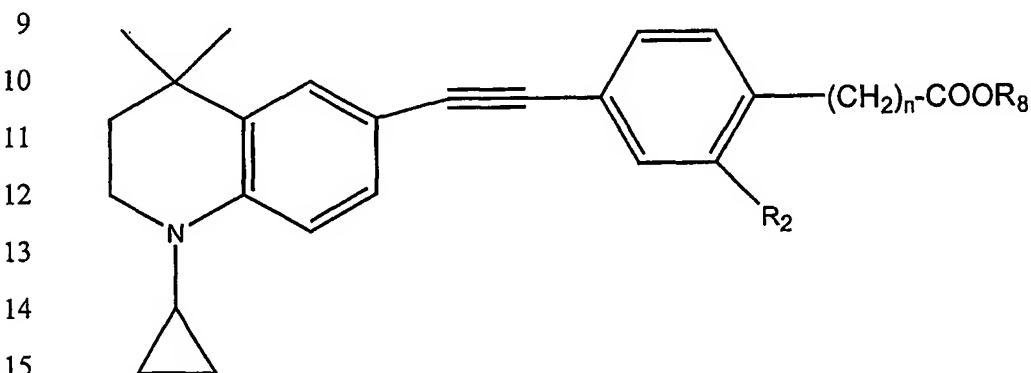
1 R_4 is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
2 alkyl of 1 to 6 carbons, or halogen;

3 o is an integer having the values of 0 to 4;

4 n is an integer having the values of 0 to 4, and

5 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
6 pharmaceutically acceptable base.

7 38. A method in accordance with Claim 37 where the compound has
8 the formula



16 wherein R_2 is hydrogen, alkyl of 1 to 6 carbons, or halogen

17 n is 0 or 1, and

18 R_8 is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
19 acceptable base.

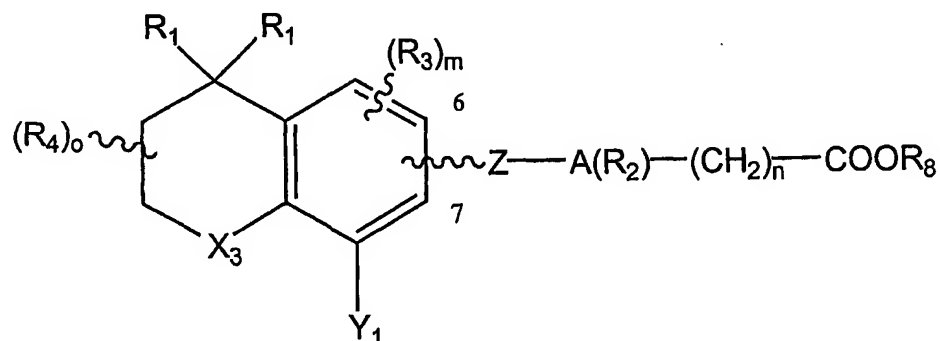
20 39. A method in accordance with Claim 38 where the compound is 4-
21 (1-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl-ethynyl)-benzoic
22 acid or a salt of said compound with a pharmaceutically acceptable base or a
23 C_{1-6} alkyl ester of said compound.

24 40. A method in accordance with Claim 38 where the compound is
25 [4-(1-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-
26 ethynyl)phenyl] acetic acid methyl ester.

27 41. A method of inhibiting the enzyme cytochrome P450RAI in a
28 mammal by administering to said mammal an effective dose of a

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1 pharmaceutical composition comprising a compound of the formula



9 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a
 10 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
 11 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl
 12 groups being optionally substituted with one or two R₂ groups;

13 X₃ is S, or O, C(R₁)₂, or CO;

14 Y₁ is H, lower alkyl of 1 to 3 carbons, cycloalkyl of 3 to 6 carbons,
 15 benzyl, lower alkyl substituted cycloalkyl of 3 to 6 carbons;

16 Z is -C≡C-,

17 -(CR₁=CR₁)_n, where n' is an integer having the value 1 - 5,

18 -CO-NR₁-,

19 NR₁-CO-,

20 -CO-O-,

21 -O-CO-,

22 -CS-NR₁-,

23 NR₁-CS-,

24 -CO-S-,

25 -S-CO-,

26 -N=N-;

27 R₁ is independently H or alkyl of 1 to 6 carbons;

28 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro

1 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
2 to 6 carbons;

3 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro
4 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio
5 of 1 to 6 carbons or benzyl;

6 m is an integer having the values 0 to 2;

7 R_4 is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
8 alkyl of 1 to 6 carbons, or halogen;

9 o is an integer having the values of 0 to 4;

10 n is an integer having the values of 0 to 4, and

11 R_8 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a
12 pharmaceutically acceptable base, the compound meeting at least one of the
13 provisos selected from the group consisting of:

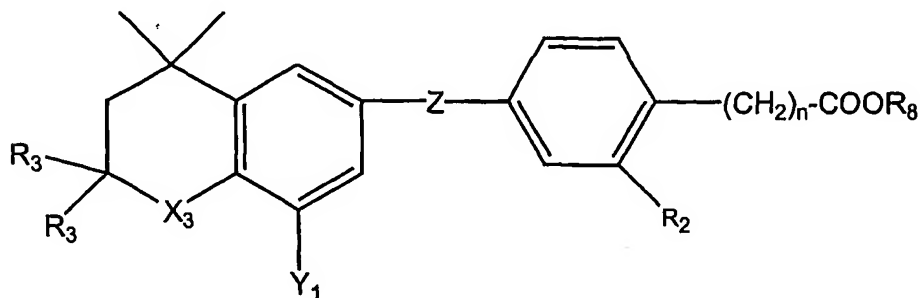
14 Y_1 is cycloalkyl,

15 when Y_1 is not cycloalkyl then X_3 is O or S and n is 1,

16 when Y_1 is not cycloalkyl then X_3 is CO, and n is 1,

17 when Y_1 is not cycloalkyl then X_3 is CO and the moiety A is
18 substituted with at least one F group.

19 42. A method in accordance with Claim 41 where the compound has
20 the formula



27 wherein R_2 is H or F;

28 R_3 is H or lower alkyl of 1 to 6 carbons;

- 1 X₃ is O or CO;
2 Y₁ is H, alkyl of 1 to 6 carbons, or cyclopropyl;
3 Z is -C≡C- or -CO-O-;
4 n is 0 or 1, and
5 R₈ is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
6 acceptable base, the compound meeting at least one of the provisos selected
7 from the group consisting of:
8 Y₁ is cyclopropyl,
9 when Y₁ is not cyclopropyl then X₃ is O and n is 1,
10 when Y₁ is not cyclopropyl then X₃ is CO, and n is 1,
11 when Y₁ is not cyclopropyl then X₃ is CO and the moiety A is
12 substituted with at least one F group.
- 13 43. A method in accordance with Claim 42 where the compound is 2-
14 fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
15 benzoic acid or a salt of said compound with a pharmaceutically acceptable
16 base or a C₁₋₆ alkyl ester of said compound.
- 17 44. A method in accordance with Claim 42 where the compound is
18 selected from the group consisting of 4-[(8,8-dimethyl-5-oxo-5,6,7,8-
19 tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid and [2-fluoro-4-
20 (8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)phenyl]-
21 acetic acid or a salt of said compound with a pharmaceutically acceptable
22 base or a C₁₋₆ alkyl ester of said compound.
- 23 45. A method in accordance with Claim 42 where the compound is 2-
24 fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid or a salt of
25 said compound with a pharmaceutically acceptable base or a C₁₋₆ alkyl ester of
26 said compound.
- 27 46. A method in accordance with Claim 42 where the compound is
28 selected from the group consisting of [4-(2,2,4,4-tetramethyl-chroman-6-yl-

1 ethynyl) phenyl] acetic acid, [2-fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-
2 ethynyl) phenyl] acetic acid and [4-(8-ethyl-2,2,4,4-tetramethyl-chroman-6-yl-
3 ethynyl) phenyl] acetic acid or a salt of said compound with a
4 pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said compound.

5 **47.** A method in accordance with Claim 42 where the compound is 4-
6 (8-cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid or a
7 salt of said compound with a pharmaceutically acceptable base or a C₁₋₆ alkyl
8 ester of said compound.

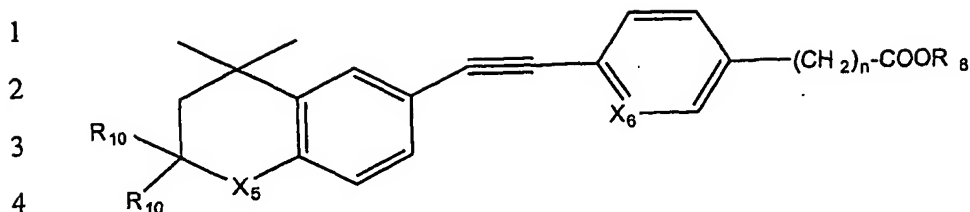
9 **48.** A method in accordance with Claim 42 where the compound is
10 selected from the group consisting of [4-(8-cyclopropyl-2,2,4,4-tetramethyl-
11 chroman-6-yl-ethynyl) phenyl] acetic acid and [4-(8-cyclopropyl-2,2,4,4-
12 tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl] acetic acid or a salt of
13 said compound with a pharmaceutically acceptable base or a C₁₋₆ alkyl ester of
14 said compound.

15 **49.** A method in accordance with Claim 42 where the compound is
16 8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid-4-
17 (carboxymethyl)phenyl ester or a salt of said compound with a
18 pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said compound.

19 **50.** A method in accordance with Claim 42 where the compound is
20 2,2,4,4-tetramethyl-chroman-6-carboxylic acid 4-(carboxymethyl)phenyl ester
21 or a salt of said compound with a pharmaceutically acceptable base or a C₁₋₆
22 alkyl ester of said compound.

23 **51.** A method of inhibiting the enzyme cytochrome P450RAI in a
24 mammal by administering to said mammal an effective dose of a
25 pharmaceutical composition comprising a compound selected from the group
26 of compounds wherein the variables for each compound are defined as
27 follows with reference to the formula below:

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5 X_5 is O, X_6 is CH, n is 0 and R_8 is H, alkyl of 1 to 6 carbons, -
6 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base;

7 X_5 is S, X_6 is CH, n is 1 and R_8 is H, alkyl of 1 to 6 carbons, -
8 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base;

9 X_5 is S, X_6 is CH, n is 2 and R_8 is H, alkyl of 1 to 6 carbons, -
10 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base;

11 X_5 is S, X_6 is CH, n is 0 and R_8 is H, alkyl of 1 to 6 carbons, -
12 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base; and

13 X_5 is S, X_6 is N, n is 0 and R_8 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base.

15 **52.** A method in accordance with Claim 51 wherein the compound is
16 selected from the group of compounds wherein the variables for each
17 compound are defined as follows:

18 X_5 is O, X_6 is CH, n is 0 and R_8 is H or a cation of a pharmaceutically
19 acceptable base;

20 X_5 is S, X_6 is CH, n is 1 and R_8 is H or a cation of a pharmaceutically
21 acceptable base;

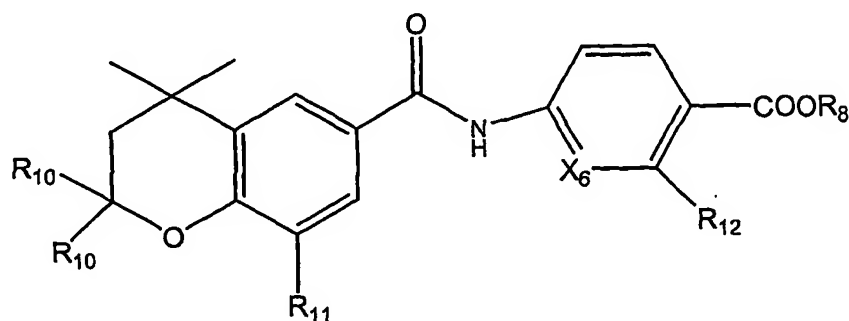
22 X_5 is S, X_6 is CH, n is 2 and R_8 is H or a cation of a pharmaceutically
23 acceptable base;

24 X_5 is S, X_6 is CH, n is 0 and R_8 is H or a cation of a pharmaceutically
25 acceptable base; and

26 X_5 is S, X_6 is N, n is 0 and R_8 is H or a cation of a pharmaceutically
27 acceptable base.

28 **53.** A method of inhibiting the enzyme cytochrome P450RAI in a

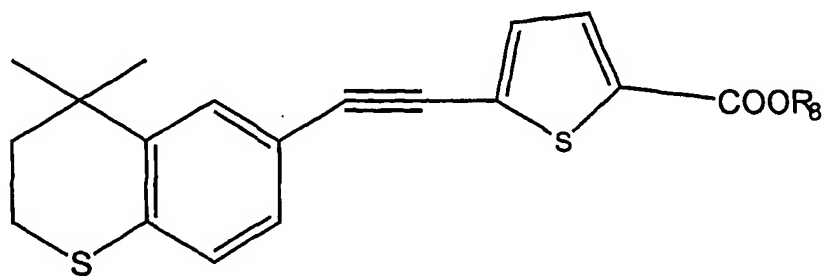
1 mammal by administering to said mammal an effective dose of a
 2 pharmaceutical composition comprising a compound shown by the formula



10 wherein the variable R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}$ -
 11 alkyl), or a cation of a pharmaceutically acceptable base.

12 54. A method in accordance with Claim 53 wherein in the formula of
 13 the compound R_8 is H or a cation of a pharmaceutically acceptable base.

14 55. A method of inhibiting the enzyme cytochrome P450RAI in a
 15 mammal by administering to said mammal an effective dose of a
 16 pharmaceutical composition comprising a compound selected from the group
 17 of compounds wherein the variables for each compound are defined as
 18 follows with reference to the formula below:



25 R_{10} is CH_3 , R_{11} is Cl, R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1 to 6
 26 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}$ -alkyl), or a cation of a pharmaceutically acceptable
 27 base;

28 R_{10} is CH_3 , R_{11} is cyclopropyl, R_{12} is F, X_6 is CH and R_8 is H, alkyl of

1 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
2 acceptable base;

3 R_{10} is CH_3 , R_{11} is CF_3 , R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1 to 6
4 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
5 base;

6 R_{10} is CH_3CH_2 , R_{11} is Br, R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1
7 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
8 base;

9 R_{10} is CH_3 , R_{11} is CH_3 , R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1 to 6
10 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
11 base;

12 R_{10} is CH_3 , R_{11} is Cl, R_{12} is F, X_6 is N and R_8 is H, alkyl of 1 to 6
13 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
14 base;

15 R_{10} is CH_3 , R_{11} is phenyl, R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1 to
16 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
17 base;

18 R_{10} is H, R_{11} is Br, R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1 to 6
19 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
20 base;

21 R_{10} is CH_3 , R_{11} is OCH_3 , R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1 to 6
22 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
23 base;

24 R_{10} is CH_3 , R_{11} is CH_3 , R_{12} is H, X_6 is CH and R_8 is H, alkyl of 1 to 6
25 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
26 base;

27 R_{10} is CH_3 , R_{11} is H, R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1 to 6
28 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable

1 base;

2 R_{10} is CH_3 , R_{11} is Br, R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1 to 6
3 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
4 base;

5 R_{10} is CH_3 , R_{11} is CF_3CF_2 , R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1
6 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
7 base;

8 R_{10} is CH_3 , R_{11} is CH_3CH_2 , R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1
9 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
10 base;

11 R_{10} is CH_3 , R_{11} is *iso*-propyl, R_{12} is F, X_6 is CH and R_8 is H, alkyl of 1
12 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable
13 base;

14 R_{10} is CH_3 , R_{11} is (1-methyl)cyclopropyl, R_{12} is F, X_6 is CH and R_8 is
15 H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a
16 pharmaceutically acceptable base;

17 R_{10} is CH_3 , R_{11} is *tertiary*-butyl, R_{12} is F, X_6 is CH and R_8 is H, alkyl
18 of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
19 acceptable base;

20 R_{10} is CH_3 , R_{11} is (2,2-difluoro)cyclopropyl, R_{12} is F, X_6 is CH and R_8
21 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a
22 pharmaceutically acceptable base and

23 R_{10} is CH_3 , R_{11} is (cyclopropyl)methyl, R_{12} is F, X_6 is CH and R_8 is H,
24 alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
25 acceptable base.

26 **56.** A method in accordance with Claim 55 wherein the compound is
27 selected from the group of compounds wherein the variables for each
28 compound are defined as follows:

- 1 R_{10} is CH_3 , R_{11} is Cl, R_{12} is F, X_6 is CH and R_8 is H or a cation of a
2 pharmaceutically acceptable base;
- 3 R_{10} is CH_3 , R_{11} is cyclopropyl, R_{12} is F, X_6 is CH and R_8 is H or a
4 cation of a pharmaceutically acceptable base;
- 5 R_{10} is CH_3 , R_{11} is CF_3 , R_{12} is F, X_6 is CH and R_8 is H or a cation of a
6 pharmaceutically acceptable base;
- 7 R_{10} is CH_3CH_2 , R_{11} is Br, R_{12} is F, X_6 is CH and R_8 is H or a cation
8 of a pharmaceutically acceptable base;
- 9 R_{10} is CH_3 , R_{11} is CH_3 , R_{12} is F, X_6 is CH and R_8 is H or a cation of a
10 pharmaceutically acceptable base;
- 11 R_{10} is CH_3 , R_{11} is Cl, R_{12} is F, X_6 is N and R_8 is H or a cation of a
12 pharmaceutically acceptable base;
- 13 R_{10} is CH_3 , R_{11} is phenyl, R_{12} is F, X_6 is CH and R_8 is H or a cation of
14 a pharmaceutically acceptable base;
- 15 R_{10} is H, R_{11} is Br, R_{12} is F, X_6 is CH and R_8 is H or a cation of a
16 pharmaceutically acceptable base;
- 17 R_{10} is CH_3 , R_{11} is OCH_3 , R_{12} is F, X_6 is CH and R_8 is H or a cation of
18 a pharmaceutically acceptable base;
- 19 R_{10} is CH_3 , R_{11} is CH_3 , R_{12} is H, X_6 is CH and R_8 is H or a cation of a
20 pharmaceutically acceptable base;
- 21 R_{10} is CH_3 , R_{11} is H, R_{12} is F, X_6 is CH and R_8 is H or a cation of a
22 pharmaceutically acceptable base;
- 23 R_{10} is CH_3 , R_{11} is Br, R_{12} is F, X_6 is CH and R_8 is H or a cation of a
24 pharmaceutically acceptable base;
- 25 R_{10} is CH_3 , R_{11} is CF_3CF_2 , R_{12} is F, X_6 is CH and R_8 is H or a cation
26 of a pharmaceutically acceptable base;
- 27 R_{10} is CH_3 , R_{11} is CH_3CH_2 , R_{12} is F, X_6 is CH and R_8 is H or a cation
28 of a pharmaceutically acceptable base;

1 R_{10} is CH_3 , R_{11} is *iso*-propyl, R_{12} is F, X_6 is CH and R_8 is H or a cation
2 of a pharmaceutically acceptable base;

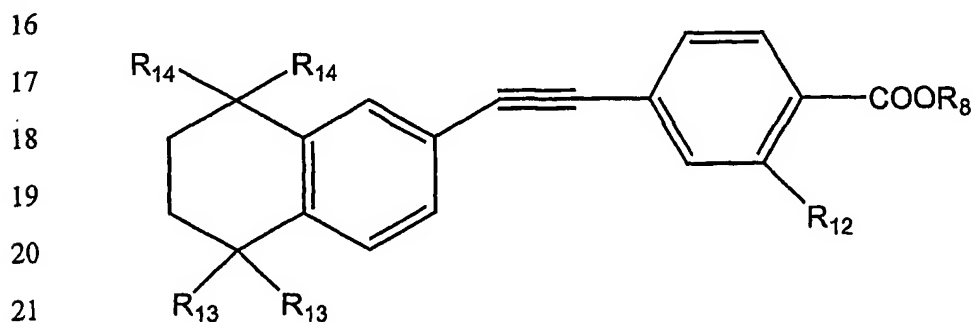
3 R_{10} is CH_3 , R_{11} is (1-methyl)cyclopropyl, R_{12} is F, X_6 is CH and R_8 is
4 H or a cation of a pharmaceutically acceptable base;

5 R_{10} is CH_3 , R_{11} is *tertiary*-butyl, R_{12} is F, X_6 is CH and R_8 is H or a
6 cation of a pharmaceutically acceptable base;

7 R_{10} is CH_3 , R_{11} is (2,2-difluoro)cyclopropyl, R_{12} is F, X_6 is CH and R_8
8 is H or a cation of a pharmaceutically acceptable base, and

9 R_{10} is CH_3 , R_{11} is (cyclopropyl)methyl, R_{12} is F, X_6 is CH and R_8 is H
10 or a cation of a pharmaceutically acceptable base.

11 57. A method of inhibiting the enzyme cytochrome P450RAI in a
12 mammal by administering to said mammal an effective dose of a
13 pharmaceutical composition comprising a compound selected from the group
14 of compounds wherein the variables for each compound are defined as follows
15 with reference to the formula below:



23 R_{12} is H, the two R_{13} groups jointly represent an oxo ($=O$) function and
24 R_{14} is CH_3 and R_8 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a
25 cation of a pharmaceutically acceptable base;

26 R_{12} is H, R_{13} is H, R_{14} is CH_3 and R_8 is H, alkyl of 1 to 6 carbons, -
27 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base;

28 R_{12} is H, R_{13} is CH_3 , R_{14} is CH_3 and R_8 is H, alkyl of 1 to 6 carbons, -

1 CH₂O(C₁₋₆-alkyl), or a cation of a pharmaceutically acceptable base;
2 R₁₂ is H, R₁₃ is CH₃, R₁₄ is H and R₈ is H, alkyl of 1 to 6 carbons, -
3 CH₂O(C₁₋₆-alkyl), or a cation of a pharmaceutically acceptable base;
4 R₁₂ is F, R₁₃ is CH₃, R₁₄ is CH₃ and R₈ is H, alkyl of 1 to 6 carbons, -
5 CH₂O(C₁₋₆-alkyl), or a cation of a pharmaceutically acceptable base, and
6 R₁₂ is H, one of the R₁₃ groups is H, the other is OH, R₁₄ is CH₃ and
7 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
8 pharmaceutically acceptable base.

9 58. A method in accordance with Claim 57 wherein the compound is
10 selected from the group of compounds wherein the variables for each
11 compound are defined as follows:

12 R₁₂ is H, the two R₁₃ groups jointly represent an oxo (=O) function and
13 R₁₄ is CH₃ and R₈ is H or a cation of a pharmaceutically acceptable base;

14 R₁₂ is H, R₁₃ is H, R₁₄ is CH₃ and R₈ is H or a cation of a
15 pharmaceutically acceptable base;

16 R₁₂ is H, R₁₃ is CH₃, R₁₄ is CH₃ and R₈ is H or a cation of a
17 pharmaceutically acceptable base;

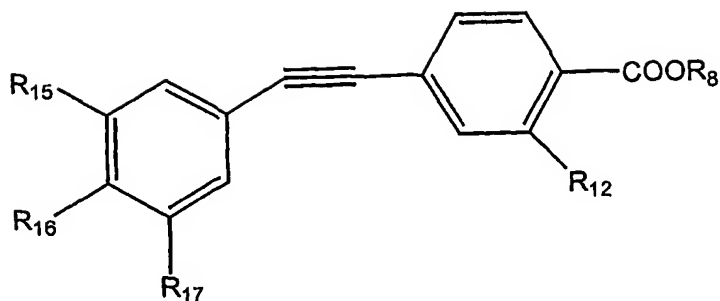
18 R₁₂ is H, R₁₃ is CH₃, R₁₄ is H and R₈ is H or a cation of a
19 pharmaceutically acceptable base;

20 R₁₂ is F, R₁₃ is CH₃, R₁₄ is CH₃ and R₈ is H or a cation of a
21 pharmaceutically acceptable base, and

22 R₁₂ is H, one of the R₁₃ groups is H, the other is OH, R₁₄ is CH₃ and
23 R₈ is H or a cation of a pharmaceutically acceptable base.

24 59. A method of inhibiting the enzyme cytochrome P450RAI in a
25 mammal by administering to said mammal an effective dose of a
26 pharmaceutical composition comprising a compound selected from the group
27 of compounds wherein the variables for each compound are defined as
28 follows with reference to the formula below:

276



R₁₂ is H, **R₁₅** is *tertiary*-butyl, **R₁₆** is OH, **R₁₇** is Cl and **R₈** is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a pharmaceutically acceptable base;

R₁₂ is H, **R₁₅** is *tertiary*-butyl, **R₁₆** is OCH₃, **R₁₇** is *tertiary*-butyl and **R₈** is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a pharmaceutically acceptable base;

R₁₂ is H, **R₁₅** is 1-adamantyl, **R₁₆** is OCH₃, **R₁₇** is H and **R₈** is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a pharmaceutically acceptable base;

R₁₂ is H, **R₁₅** is *tertiary*-butyl, **R₁₆** is OH, **R₁₇** is *tertiary*-butyl and **R₈** is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a pharmaceutically acceptable base, and

R₁₂ is F, **R₁₅** is *tertiary*-butyl, **R₁₆** is OH, **R₁₇** is H and **R₈** is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a pharmaceutically acceptable base.

60. A method in accordance with Claim 59 wherein the compound is selected from the group of compounds wherein the variables for each compound are defined as follows:

R₁₂ is H, **R₁₅** is *tertiary*-butyl, **R₁₆** is OH, **R₁₇** is Cl and **R₈** is H or a cation of a pharmaceutically acceptable base;

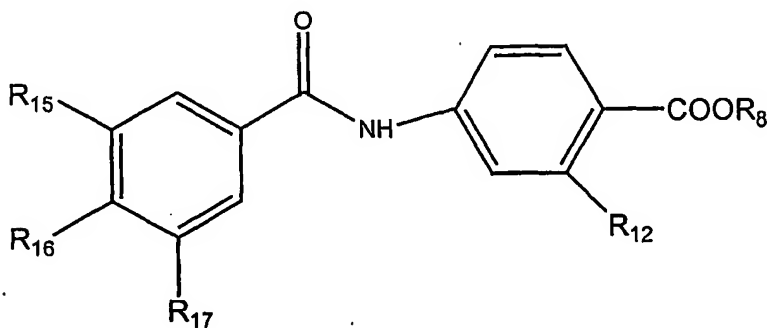
R₁₂ is H, **R₁₅** is *tertiary*-butyl, **R₁₆** is OCH₃, **R₁₇** is *tertiary*-butyl and **R₈** is H or a cation of a pharmaceutically acceptable base;

1 R_{12} is H, R_{15} is 1-adamantyl, R_{16} is OCH_3 , R_{17} is H and R_8 is H or a
2 cation of a pharmaceutically acceptable base;

3 R_{12} is H, R_{15} is *tertiary*-butyl, R_{16} is OH, R_{17} is *tertiary*-butyl and R_8
4 is H or a cation of a pharmaceutically acceptable base, and

5 R_{12} is F, R_{15} is *tertiary*-butyl, R_{16} is OH, R_{17} is H and R_8 is H or a
6 cation of a pharmaceutically acceptable base.

7 61. A method of inhibiting the enzyme cytochrome P450RAI in a
8 mammal by administering to said mammal an effective dose of a
9 pharmaceutical composition comprising a compound selected from the group
10 of compounds wherein the variables for each compound are defined as
11 follows with reference to the formula below:



19 R_{12} is F, R_{15} is *tertiary*-butyl, R_{16} is CH_3CH_2O , R_{17} is I and R_8 is H,
20 alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
21 acceptable base, and

22 R_{12} is F, R_{15} is *tertiary*-butyl, R_{16} is CH_3CH_2O , R_{17} is Br and R_8 is H,
23 alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically
24 acceptable base.

25 62. A method in accordance with Claim 61 wherein the compound is
26 selected from the group of compounds wherein the variables for each
27 compound are defined as follows:

28 R_{12} is F, R_{15} is *tertiary*-butyl, R_{16} is CH_3CH_2O , R_{17} is I and R_8 is H or

1 a cation of a pharmaceutically acceptable base, and

2 R_{12} is F, R_{15} is *tertiary*-butyl, R_{16} is CH_3CH_2O , R_{17} is Br and R_8 is H

3 or a cation of a pharmaceutically acceptable base.

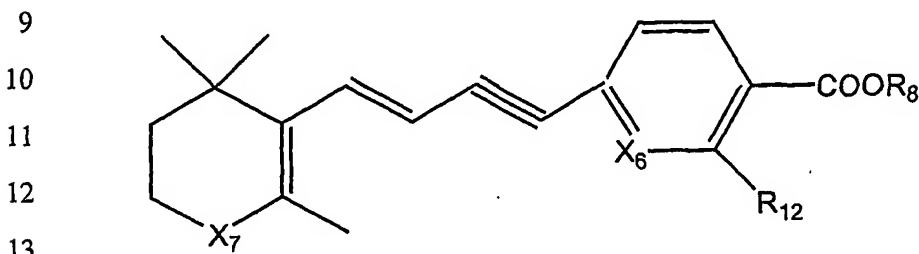
4 63. A method of inhibiting the enzyme cytochrome P450RAI in a

5 mammal by administering to said mammal an effective dose of a

6 pharmaceutical composition comprising a compound selected from the group

7 of compounds wherein the variables for each compound are defined as

8 follows with reference to the formula below:



14 R_{12} is H, X_6 is CH, X_7 is $(CH_3)_2C$ and R_8 is H, alkyl of 1 to 6 carbons,
15 $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base;

16 R_{12} is H, X_6 is CH, X_7 is CH_2 and R_8 is H, alkyl of 1 to 6 carbons, -
17 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base;

18 R_{12} is H, X_6 is CH, X_7 is S and R_8 is H, alkyl of 1 to 6 carbons, -
19 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base;

20 R_{12} is F, X_6 is CH, X_7 is CH_2 and R_8 is H, alkyl of 1 to 6 carbons, -
21 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base, and

22 R_{12} is H, X_6 is N, X_7 is CH_2 and R_8 is H, alkyl of 1 to 6 carbons, -
23 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base.

24 64. A method in accordance with Claim 63 wherein the compound is

25 selected from the group of compounds wherein the variables for each

26 compound are defined as follows:

27 R_{12} is H, X_6 is CH, X_7 is $(CH_3)_2C$ and R_8 is H or a cation of a

28 pharmaceutically acceptable base;

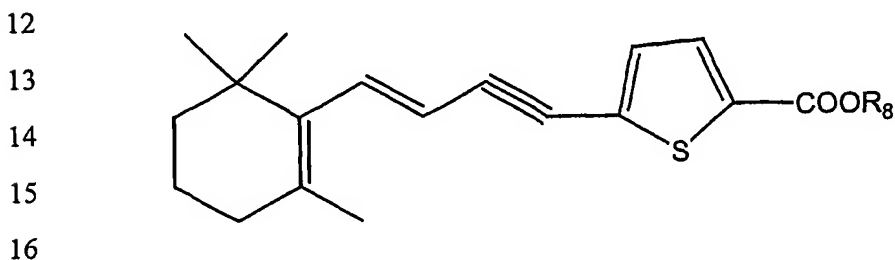
1 R_{12} is H, X_6 is CH, X_7 is CH_2 and R_8 is H or a cation of a
2 pharmaceutically acceptable base;

3 R_{12} is H, X_6 is CH, X_7 is S and R_8 is H or a cation of a
4 pharmaceutically acceptable base;

5 R_{12} is F, X_6 is CH, X_7 is CH_2 and R_8 is H or a cation of a
6 pharmaceutically acceptable base, and

7 R_{12} is H, X_6 is N, X_7 is CH_2 and R_8 is H or a cation of a
8 pharmaceutically acceptable base.

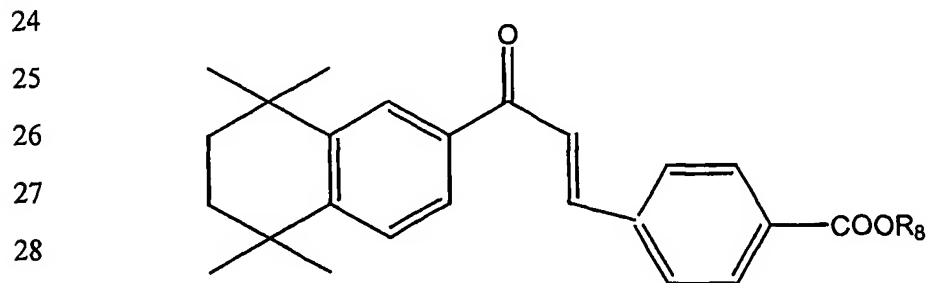
9 65. A method of inhibiting the enzyme cytochrome P450RAI in a
10 mammal by administering to said mammal an effective dose of a
11 pharmaceutical composition comprising a compound shown by the formula



17 wherein the variable R_8 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}-$
18 alkyl), or a cation of a pharmaceutically acceptable base.

19 66. A method in accordance with Claim 65 wherein in the formula of
20 the compound R_8 is H or a cation of a pharmaceutically acceptable base.

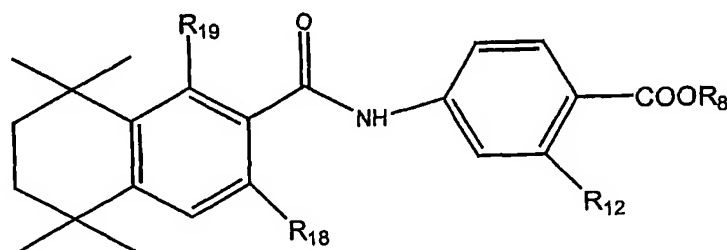
21 67. A method of inhibiting the enzyme cytochrome P450RAI in a
22 mammal by administering to said mammal an effective dose of a
23 pharmaceutical composition comprising a compound shown by the formula



1 wherein the variable R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}$ -
2 alkyl), or a cation of a pharmaceutically acceptable base.

3 68. A method in accordance with Claim 67 wherein in the formula of
4 the compound R_8 is H or a cation of a pharmaceutically acceptable base.

5 69. A method of inhibiting the enzyme cytochrome P450RAI in a
6 mammal by administering to said mammal an effective dose of a
7 pharmaceutical composition comprising a compound selected from the group
8 of compounds wherein the variables for each compound are defined as
9 follows with reference to the formula below:



16 R_{12} is F, R_{18} is H, R_{19} is H and R_8 is H, alkyl of 1 to 6 carbons, -
17 $\text{CH}_2\text{O}(\text{C}_{1-6}$ -alkyl), or a cation of a pharmaceutically acceptable base, and

18 R_{12} is H, R_{18} is OH, R_{19} is F and R_8 is H, alkyl of 1 to 6 carbons, -
19 $\text{CH}_2\text{O}(\text{C}_{1-6}$ -alkyl), or a cation of a pharmaceutically acceptable base.

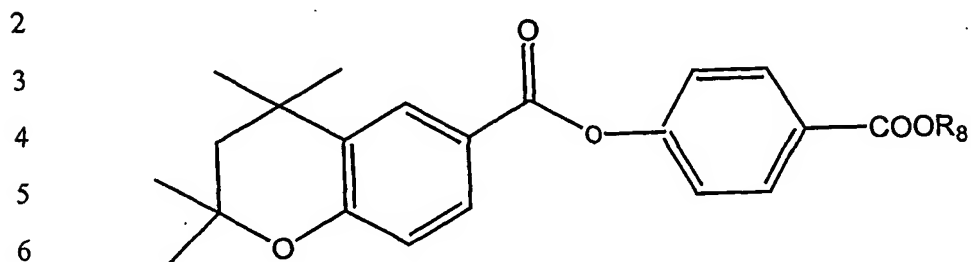
20 70. A method in accordance with Claim 69 wherein the compound is
21 selected from the group of compounds wherein the variables for each
22 compound are defined as follows:

23 R_{12} is F, R_{18} is H, R_{19} is H and R_8 is H or a cation of a
24 pharmaceutically acceptable base, and

25 R_{12} is H, R_{18} is OH, R_{19} is F and R_8 is H or a cation of a
26 pharmaceutically acceptable base.

27 71. A method of inhibiting the enzyme cytochrome P450RAI in a
28 mammal by administering to said mammal an effective dose of a

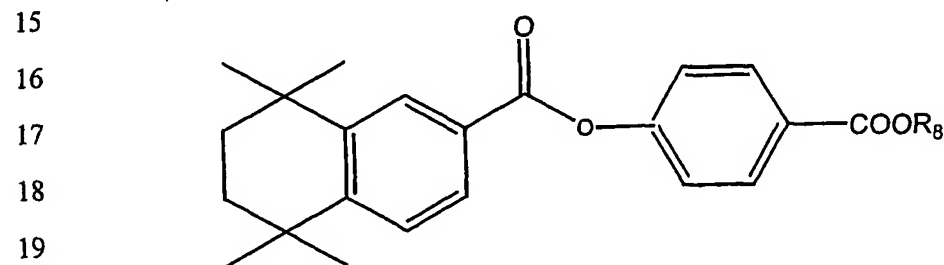
1 pharmaceutical composition comprising a compound shown by the formula



8 wherein the variable R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}$
9 alkyl), or a cation of a pharmaceutically acceptable base.

10 72. A method in accordance with Claim 71 wherein in the formula of
11 the compound R_8 is H or a cation of a pharmaceutically acceptable base.

12 73. A method of inhibiting the enzyme cytochrome P450RAI in a
13 mammal by administering to said mammal an effective dose of a
14 pharmaceutical composition comprising a compound shown by the formula

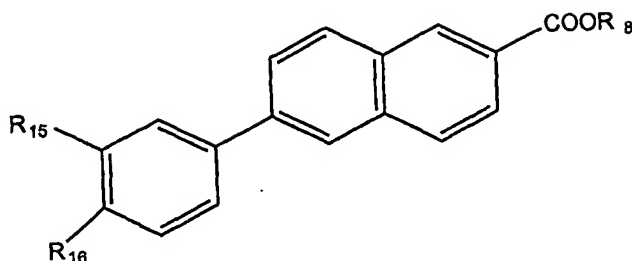


21 wherein the variable R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}$
22 alkyl), or a cation of a pharmaceutically acceptable base.

23 74. A method in accordance with Claim 73 wherein in the formula of
24 the compound R_8 is H or a cation of a pharmaceutically acceptable base.

25 75. A method of inhibiting the enzyme cytochrome P450RAI in a
26 mammal by administering to said mammal an effective dose of a
27 pharmaceutical composition comprising a compound selected from the group
28 of compounds wherein the variables for each compound are defined as

1 follows with reference to the formula below:



8 R_{15} is 1-adamantyl, R_{16} is OH and R_8 is H, alkyl of 1 to 6 carbons, -
9 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base, and

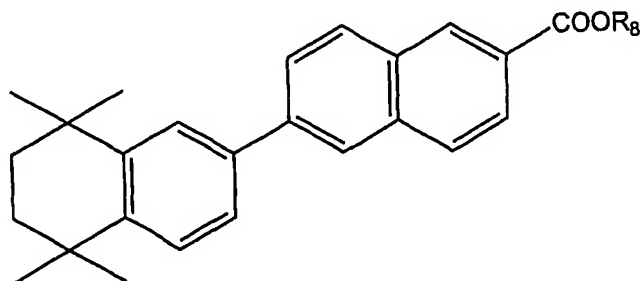
10 R_{15} is 1-adamantyl, R_{16} is OCH_3 and R_8 is H, alkyl of 1 to 6 carbons, -
11 $CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a pharmaceutically acceptable base.

12 76. A method in accordance with Claim 75 wherein the compound is
13 selected from the group of compounds wherein the variables for each
14 compound are defined as follows:

15 R_{15} is 1-adamantyl, R_{16} is OH and R_8 is H or a cation of a
16 pharmaceutically acceptable base, and

17 R_{15} is 1-adamantyl, R_{16} is OCH_3 and R_8 is H or a cation of a
18 pharmaceutically acceptable base.

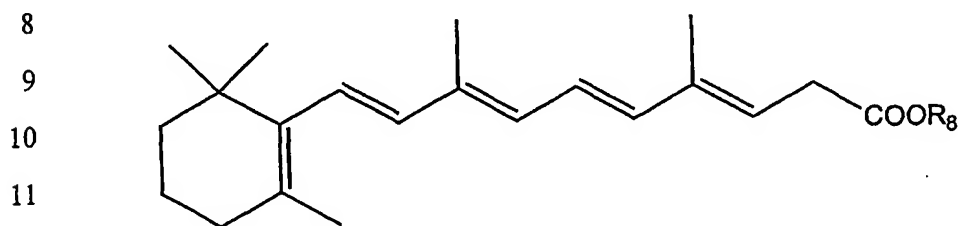
19 77. A method of inhibiting the enzyme cytochrome P450RAI in a
20 mammal by administering to said mammal an effective dose of a
21 pharmaceutical composition comprising a compound shown by the formula



1 wherein the variable R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}$
 2 alkyl), or a cation of a pharmaceutically acceptable base.

3 78. A method in accordance with Claim 77 wherein in the formula of
 4 the compound R_8 is H or a cation of a pharmaceutically acceptable base.

5 79. A method of inhibiting the enzyme cytochrome P450RAI in a
 6 mammal by administering to said mammal an effective dose of a
 7 pharmaceutical composition comprising a compound shown by the formula



13 wherein the variable R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}$
 14 alkyl), or a cation of a pharmaceutically acceptable base.

15 80. A method in accordance with Claim 79 wherein in the formula of
 16 the compound R_8 is H or a cation of a pharmaceutically acceptable base.

17 81. A method of providing a compound which is an inhibitor of the
 18 enzyme cytochrome P450RAI, the method comprising:

19 identifying a compound that has activity as a retinoid in an art
 20 recognized assay which demonstrates retinoid-like activity, the retinoid
 21 compound having a formula such that it includes a benzoic acid, benzoic acid
 22 ester, naphthoic acid, naphthoic acid ester or heteroaryl carboxylic acid or
 23 ester moiety, with a partial structure of $-\text{A}(\text{R}_2)-(\text{CH}_2)_n-\text{COOR}_8$ where n is
 24 0, A is a phenyl or naphthyl group, or heteroaryl selected from a group
 25 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
 26 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl, naphthyl and
 27 heteroaryl groups being optionally substituted with one or two R_2 groups; R_2
 28 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro substituted

1 alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons
2 and R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
3 pharmaceutically acceptable base, and

4 selecting a compound that is a homolog of the previously identified
5 retinoid compound where in the formula of the homolog n is 1 or 2.

6 **82.** A method in accordance with Claim 81 wherein a homolog is
7 selected where in the formula of the homolog n is 1.

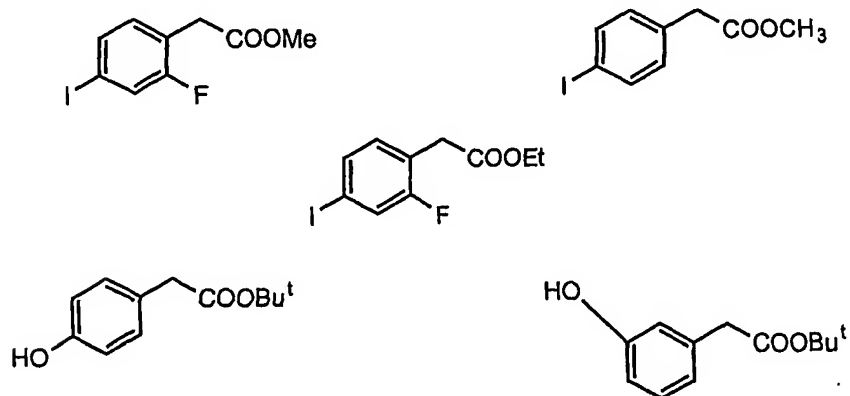
8 **83.** A method in accordance with Claim 81 further comprising the step
9 of synthesizing the selected homolog.

10 **84.** A method in accordance with Claim 83 wherein a homolog is
11 synthesized where in the formula of the homolog n is 1.

12 **85.** A method in accordance with Claim 83 wherein the step of
13 synthesizing the homolog utilizes a homologation procedure wherein a chain
14 of a carboxylic acid or of carboxylic ester of the partial formula $-\text{A}(\text{R}_2)-$
15 $(\text{CH}_2)_n-\text{COOR}_3$ is lengthened by adding one or two (CH_2) units.

16 **86.** A method in accordance with Claim 85 wherein the step of
17 synthesizing the homolog utilizes *Arndt-Eistert* method of synthesis.

18 **87.** A method in accordance with Claim 84 where the step of
19 synthesizing the homolog includes a reaction with a reagent selected from the
20 formulas



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